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EFFECT OF HEIDELBERG SCALP ACUPUNCTURE ON THE COGNITIVE FUNCTION OF MILD TO MODERATE ALZHEIMER'S DISEASE PATIENTS -A PRELIMINARY STUDY

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Resumo

Enquadramento

Cerca de 2 a 8% dos indivíduos acima dos 60 anos de idade sofrem de alguma forma de Demência, de entre as quais a Doença de Alzheimer (DA) é a mais comum. Até ao presente, a doença não tem cura, exercendo uma enorme pressão sobre os custos dos serviços sociais de saúde de cada país - é a sexta maior causa de morte nos Estados Unidos e representa mais da metade de todos os casos de demência, que se estimam vir quadruplicar nas próximas quatro décadas.

Objectivos

A Acupunctura Craniana de Heidelberg (ACH) é um novo sistema somatotópico de acupunctura, tendo por base a existência de correlações entre pontos específicos localizados no escalpe, funções fisiológicas e regiões anatómicas. Com suporte em experiências anteriores, propomos desenvolver um protocolo de estudo, envolvendo o tratamento de pacientes portadores da Doença de Alzheimer, através da ACH, avaliando o potencial benefício em termos da evolução da função cognitiva, medida através do recurso a testes psicométricos, nomeadamente a Avaliação Breve do Estado Mental (ABEM) e à vertente cognitiva da Escala de Avaliação da Doença de Alzheimer (EADA).
Propomos no final uma abordagem metodológica para comparar a eficácia da terapia combinada (ACH + terapia farmacológica) vs terapia farmacológica, na função cognitiva de doentes de Alzheimer.

Métodos

Depois de obtido parecer positivo por parte da Comissão de Ética do ICBAS-UP, foram contactados catorze pacientes diagnosticados com DA por um neurologista independente. Seis desses sujeitos (idade média de 78.5 anos), aceitaram o convite para fazer parte de um estudo preliminar e, após o consentimento informado, foram aplicadas e retidas por um período de 3 dias, sete agulhas permanentes (gold) nos apelidados *sete chakras*. Como parte dos critérios de inclusão, foi solicitado ao seu médico responsável a não alteração da medicação durante o período de experiência.

Resultados

Após administração da ACH, verificámos melhorias nos resultados de testes em cinco dos seis pacientes que incorporaram o estudo. No que respeita à ABEM o aumento médio foi de 3,83 pontos (4.36dp) e na EADA-cog, a melhoria está reflectida na redução média verificada de 4,67 pontos (5.72dp). Não foram observadas diferenças estatisticamente significativas quando comparadas as médias obtidas antes e depois da condição de tratamento. Os dados permitiram ainda a estimativa do tamanho da amostra, que neste caso deverá ser n>289.

Discussão

Apesar da ausência de significância estatística, o que em nossa opinião se fica a dever ao reduzido tamanho da amostra e aos elevados desvios-padrão verificados (algo expectável para a patologia), no presente estudo foram observadas melhorias individuais e incrementos médios impressionantes para ambos os testes.

A Acupunctura Craniana de Heidelberg parece promissora na reversão do déficit cognitivo dos pacientes com DA. O eventual mecanismo de acção da ACH na DA poderá estar relacionado com o aumento da microcirculação em algumas zonas cerebrais, no entanto, este raciocínio é puramente especulativo e deverá ser objecto de investigações futuras. Após análise estatística e qualitativa dos dados, propomos uma metodologia para um futuro ensaio clínico.

Keywords: Acupunctura Craniana de Heidelberg; Doença de Alzheimer; Avaliação Breve do Estado Mental; Escala de Avaliação da Doença de Alzheimer - sub-escala cognitiva; Acupunctura; Medicina Tradicional Chinesa; micro Acupunctura

Este texto é escrito de acordo com o antigo acordo ortográfico.

Abstract

Background

In each country 2 to 8% of the individuals above 60 years old are expected to suffer from any form of the dementia, from which Alzheimer's Disease is the most common form. This medical condition for which there is still no cure, puts a considerable amount of pressure on national health care systems facing immensely huge health care costs. The disease is already the sixth leading cause of death in the United States and it represents more than half of all Dementia cases, which are expected to quadruple over the next four decades.

Objectives

Heidelberg Scalp Acupuncture (HSA) is a novel somatotopic system of Acupuncture developed on the basis of existing correlations between specific skull acupoints, physiological functions and anatomical regions. Due to some positive personal experience with this technique, we are interested in finding whether it is possible to develop a study protocol to treat Alzheimer's Disease by HSA, and to measure the potential clinical outcome using psychometric tests - the Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog).
We further propose a methodological approach to compare the efficacy of a combined therapy (HSA and pharmacological treatment) versus pharmacological treatment alone, on the cognitive function of AD patients.

Methods

After obtaining positive feedback from the ICBAS-UP Ethical Committee, fourteen patients diagnosed with AD by an independent Neurologist were contacted. Six of these subjects (mean age 78.5 years), showed willingness to be part of a preliminary study and after informed consent, HSA was applied. Permanent scalp acupuncture gold needles were retained for a three day period in the so called *seven chakras* with no change in the patients medication occurring during the test period (part of the eligibility criteria).

Results

Out of the six patients that took part in the experiment, five have shown better values in both tests after HSA. Regarding MMSE, average increase was 3.83 points

(4.36sd) and on ADAS-cog, improvement was reflected by an average decrease of 4.67 points (5.72sd). No statistical differences were found before and after the treatment condition. The data further allowed the estimation of the sample size, which in this case should be n>289.

Discussion

Despite the absence of statistical significance, which in our opinion is due to the small sample size and high standard deviations (which is expected in this disease), we measured impressive individual and average improvements in MMSE and ADAS-cog.

Heidelberg Scalp Acupuncture showed promising results on the reversion of the cognitive deficit felt by AD patients. The mechanism by which this potential effect may take place could be an increase microcirculation within certain areas of the brain, although this remains speculative. After statistical analysis and scrutiny of recovered insights, a methodology for a future clinical trial is proposed.

Keywords: Heidelberg Scalp Acupuncture; Alzheimer's Disease; Mini Mental State Examination; Alzheimer's Disease Assessment Scale - cognitive subscale; Acupuncture; Traditional Chinese Medicine; Micro Acupuncture

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Glossary

Ach - Acetylcholine

AChE - Acetylcholinesterase

AChEi - Acetylcholinesterase Inhibitor

AD - Alzheimer's Disease

ADAS-cog - Alzheimer's Disease Assessment Scale - cognitive subscale

ADL - Activities of Daily Living

ATE - Acupoint Thread Embedding

CAT - Catalase

ChAT - CholineAcetyltransferase

CSA - Chinese Scalp Acupuncture

CSDD - Cornell Scale for Depression in Dementia

DA - Deep Acupuncture

EA - Electroacupuncture

ECIWO - Embryo Containing Information of the Whole Organism

FAQ - Family Attitude Questionnaire

fMRI - functional Magnetic Ressonance Imaging

GSH-Px - Glutathione peroxidase

HC - Healthy Controls

HDS-R - Hasegawa's Dementia Scale

HMTCM - Heidelberg Model of Traditional Chinese Medicine

HSA - Heidelberg Scalp Acupuncture

HSCMMC - Hospital da Santa Casa da Misericórdia de Marco de Canaveses

ICBAS - Instituto de Ciências Biomédicas Abel Salazar

ICD-10 - International Classification of Diseases, 10th revision

MA - Microsystems Acupuncture

MCI - Mild Cognitive Impairment

MDA - Malondialdehyde

MMSE - Mini Mental State Examination

NCCAM - National Centre for Complementary and Alternative Medicine

NCD - Neurocognitive Disorder

NICE - National Institute for Health and Clinical Excellence guidelines on Dementia

NINCDS-ADRA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now

known as the Alzheimer's Association)

OECD - Organization for Economic Co-operation and Development

PET - Positron Cumputerized tomography

RCT - Randomized Control Trials

SA - Scalp Acupuncture

SA - Superficial Acupuncture

SIR1 - Silent Information Regulator 1

SOD - Superoxide Dismutase

SPEC - Single Photon Emission Computerized Tomography

TCM - Traditional Chinese Medicine

TENS - Transcutaneous Electrical Nerve Stimulation

VD - Vascular Dementia

WHO - World Health Organization

YNSA - Yamamoto New Scalp Acupuncture

Some abbreviations appear once again within the document’s footnotes to facilitate reading.

1

INTRODUCTION

In a competitive world, survival of the fittest is key to accomplishment. Cognitive function plays a paramount role in the quality-of-life of the individual, younger or older. In younger people, as part of the learning process, the brain is continuously being stimulated and requested as a fundamental asset in the growing up, evolutionary process, and in older people, because as one grow old, brain function decreases and this progressive reduction contributes to an array of impairments that in term, may lead to increased levels of morbidity and even mortality.
One of the immediate consequences of this lack of function, can be observed on the degree of dependency that patients suffering from dementia have of another individual for the everyday tasks, leading to new social, medical and personal needs that didn't exist before the disease.
Of gradual onset, dementias are one of the major causes of disability and lack of social independency among elderly people (Alzheimer's Association 2014).

WHO[i] estimates that 35.6 million people worldwide suffer from dementia and that there are 7.7 million new cases each year, with projections to double this value every 20 years.
In each country 2 to 8% of the individuals above 60 years old are expected to suffer from any form of the dementia, from which Alzheimer is the most common, reaching to 60 to 80% of all dementia cases (Alzheimer's Association 2012, Alzheimer's Association 2013, Alzheimer's Association 2014); (OECD 2013).

In the United States of America, where estimations point to 469.000 new cases this year alone, Alzheimer's Disease is the 6th leading cause of death - one in every nine individuals aged 65 and plus have AD[ii] and every 67 seconds a new case is diagnosed, time that is expected to be reduced to 33 seconds by mid-century (Alzheimer's Association 2012, Alzheimer's Association 2013, Alzheimer's Association 2014).

When it comes to OECD[iii] (2013) state members, reporting to 2009, an estimated 14 million people over 60 years old suffer from dementia.

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i WHO - World Health Organization

ii AD - Alzheimer's Disease

iii Organization for Economic Co-operation and Development

Portuguese Alzheimer's Association (2014) reckons that a total of 90.000 people suffer from AD in this country. Acknowledging the impact of this matter within the nation's health status, the portuguese Solidarity Minister previews for 2015, the conclusion of one of the largest and more expensive studies in the nation to this day, (requiring a total of €3,6 million), with the objective to correctly identify Dementia cases and reeducate specialized technicians to cope with the disease (Sapo Saúde 2014).

The prevalence of the disease is higher in women than in men, with almost two thirds of patients with AD belonging to the female gender, what might be explained by longer life-expectancy rates of women. Some authors however (Paganini-Hill and Henderson 1994), suggest a relation between estrogen loss related to menopause, as a possible explanation to elevated rates of development of AD in women. Also when observing educational levels, it seems that people with fewer educational level may be in higher risk to develop dementias (Alzheimer's Association 2014).

Disease Costs

"AD is one of the costliest chronic disease to society"
(Alzheimer's Association 2014)

Up to date, there is no cure for AD, and the long duration of the illness from diagnosis to death - an average of six years - contributes significantly to its public health relevance (Ganguli, Dodge et al. 2005).
The economical impact is not restricted to families and relatives of affected individuals, but also concerns national health systems, morally and legally obligated to provide solutions to deal with the effects of the disease.

Alone in the USA, the direct expenditures of the nation attributed to Alzheimer's Disease, estimated by the Alzheimer's Association (2014), reached $214 billion in 2014, ($150 billion covered by Medicare and Medicaid National health systems), costs that according to Hurd et al. (2013), will yet increase to an hopping $1,2 trillion in 2050.

As AD progresses, patients tend to loose space and time references. There is a gradual loss of cognitive function and memory, often confounded by the normal progression of the aging process.
Patients become dependant of others to perform their daily activities and routines and personality and behavioral disturbances make it a challenge to act according to community and social standards. Once a kind grandmother or grandfather, husband or wife, mother or father, the AD patient gradually becomes a stigmatized, unrecognizable human being, surrounded by unfamiliar faces.

Caring for these patients rapidly becomes a full time job. A 24-7, 365 days a year task, mainly performed by non-paid family members. Despite the fact that 80% of total care among AD patients is reported as being informal and therefore non paid, these caregivers are left with a huge invoice - the oblivious human cost of the disease.
In a study with the objective to describe the mental state and needs of Dementia and Alzheimer's Disease caregivers in Portugal, França (2010) found that these group of people tend to suffer from a higher degree of symptomatology on their psychopathological profile, when compared to the general population, showing high prevalence of Anxiety levels, Depression and other mental disbalances.

Common sentences within families affected by the disease include the negative, cold blunted, "nothing can be done", where hopeless is frequently the prevailing sentiment, slowly and subtly draining emotions away.

AD cannot be considered just a family problem, but actually, also a social challenge. Worldwide population is becoming older by the second. While scientific advances contributes to increase life expectancy rates, the current social and economic conditions do not favor families with several descendants like once did. Demographic pyramids are becoming inverted, and the world's 7,6% of individuals aged 65 or older in 2010 are expected to turn into 22,3% by 2100. This in all, makes it crucial to find effective means to invert the course of this hungry resource consuming disease and renew the hope of these patients, their families and the whole community.

Since there is no cure for AD and conventional medical treatment remains limited, we want to study whether additional treatments offered by complementary therapies, such as Traditional Chinese Medicine, may represent an increased value for patients.

Acupuncture is embedded in Tradicional Chinese Medicine - one of the oldest known documented World Medicines.
Some doubts concerning its mechanism of action and effectiveness still prevail to these days. The number of studies on the subject is yet scarce, and generally methodological issues prevent clear, non dubious conclusions (Hurd, Martorell et al. 2013). Nevertheless there has been some evidence of positive effects of its usage on the treatment of Dementia and AD.

Craniopuncture or Scalp Acupuncture (SA) by its turn, can be observed as a derived form of acupuncture. Recent unpublished work by prominent german physician and TCM Professor, Greten, using the so-called Heidelberg Scalp Acupuncture (HSA) methodology on Alzheimer's Disease patients seems promising, although scientific evidence to support his findings is needed.

It is our belief that HSA might have a positive effect on reducing cognitive loss in Alzheimer's patients, thus improving these patients quality of life. Taking this into account, we will try to compare the cognitive changes observed in patients subjected to HSA plus pharmacological therapy vs those obtained when pharmacological therapy is used alone.

2

ALZHEIMER'S DISEASE

2.1

DIAGNOSIS

The diagnostic criteria for Alzheimer's Disease was initially established by Mckhann and his peers (1984) on a NINCDS-ADRDAi report. These authors categorized AD into ***Probable AD***, ***Possible AD*** and ***Definite AD*** (table 1).

Probable Alzheimer's Disease	***All of the following must be present:*** *-Dementia established by examination and documented by objective testing* *-Impairment in memory and at least one other cognitive function (e.g., language or perception)* *-Progressive worsening of memory and at least one other cognitive function* *-No disturbance in consciousness* *-Onset between 40 and 90 years of age* *-Absence of another brain disorder or systemic disease that might cause dementia* *In addition, the diagnosis may be supported by one or more of the following:* *-Loss of motor skills* *-Diminished independence in activities of daily living and altered patterns of behaviour* *-Family history of similar disorder* *-Laboratory results consistent with the diagnosis (e.g., cerebral atrophy on computed tomography)*
Possible Alzheimer's Disease	*Fulfillment of the above criteria with variation in the onset of symptoms or manifestations or in clinical course; or a single, but gradually progressive, cognitive impairment without an identifiable cause* *Another brain disorder or systemic disease that is sufficient to produce dementia, but that is not considered to be the underlying cause of the dementia in the patient*
Definite Alzheimer's Disease	*Fulfilment of the above clinical criteria and histologic evidence of Alzheimer's disease based on examination of brain tissue obtained at biopsy or autopsy*

Table 1 - Alzheimer's Disease categorization according to Mckhann et al. (1984)

AD is therefore defined as a special form of Dementia, making it rather

i NINCDS-ADRA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association)

impossible to understand this disease without firstly approaching the later concept.

Robert et al. (1994), define Dementia as a clinical syndrome of gradual onset, involving loss of intellectual functions and memory, while maintaining normal consciousness.

A more precise definition was given by the WHO (1992), on their tenth revision of the ICD[i] manual, where both Dementia as well as Alzheimer's Disease, are comprised on a block of mental disorders of common etiology, called "Mental and Behavioural Disorders":

"Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement.
Consciousness is not clouded. The impairments of cognitive functions are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in Alzheimer disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain."
(World Health Organisation 1992)

On the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), in order to precisely differentiate the disease, and eventually mitigate stigmatization issues, the American Psychiatric Association (2013) takes the definition one step further, replacing the term Dementia, previously considered an entity of its own, subsuming it under a new subject named **Major Neurocognitive Disorders (MCD)**.
The new entity is now included in a narrower category of a vast group of **Neurocognitive Disorders (NCD)**, whose primary clinical deficit is cognitive function [Delirium, Major Cognitive Disorder (MCD) and Mild Cognitive Disorder (mCD)].

i ICD-10 - International Classification of Diseases, 10th revision

Consequently, **Major Cognitive Disorder** and **Mild Cognitive Disorder** integrate Neurocognitive Disorder due to Alzheimer's Disease and some other various subtypes out of the scope of the present paper, namely: vascular NCD; NCD with Lewy bodies; NCD due to Parkinson's Disease; frontotemporal NCD; NCD due to traumatic brain injury; NCD due to HIV infection; substance/medication-induced NCD; NCD due to Huntington's disease; NCD due to prion disease; NCD due to another medical condition; NCD due to multiple etiologies; unspecified NCD (American Psychiatric Association 2013).

The establishment of the Neurocognitive Disorder is based on the patient's cognitive state, analyzed within delimited and specific cognitive domains:

-***Complex Attention*** *(sustained attention, divided attention, selective attention, processing speed);*

-***Executive Function*** *(planning, decision making, working memory, responding to feedback,/error correction, overriding habits/inhibition, mental flexibility);*

-***Learning and Memory*** *(immediate memory, recent memory [including free recall, cued recall, and recognition memory], very-long-term memory [semantic; autobiographical], implicit learning);*

-***Language*** *(expressive language [including naming, word finding, fluency, grammar, syntax and receptive language])*

-***Perceptual-Motor Abilities*** *(includes abilities subsumed under the terms visual perception, visuo-constructional perceptual-motor praxis, and gnosis),*

-***Social Cognition*** *(recognition of emotions, theory of mind).*

(American Psychiatric Association 2013)

By its turn, differentiation between **Major** and **Mild** forms of Neurocognitive Disorders occurs both at the level of a cognitive decline from a previous level of performance in one or more cognitive domains[i], as well as to the extent that those cognitive deficits interfere with normal daily activities of the patient[ii] (table 2).

i Major form usually results from significative decline, whereas Mild form is diagnosed when in presence of a modest decline

ii Major form is diagnosed when there is loss of independence whereas is Mild form the cognitive deficits do not interfere with the ability to perform everyday tasks independently

Major Cognitive Disorder (MCD) is diagnosed when the following is present:	*A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:* *1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and* *2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.* *B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).* *C. The cognitive deficits do not occur exclusively in the context of a delirium.* *D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).*
Mild Cognitive Disorder (mCD) is diagnosed when there is:	*A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:* *1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and* *2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.* *B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).* *C. The cognitive deficits do not occur exclusively in the context of a delirium.* *D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).*

Table 2 - Diagnostic criteria for Major and Mild Neurocognitive Disorder - adapted from (American Psychiatric Association - DSM-5 Task Force 2013)

AD diagnosis is therefore rather complex, and follows four major benchmarks (see table 3).

Criterion A	states that criteria for MCD or mCD is met	
Criterion B	states the insidious onset and gradual progression of the impairment in one or several cognitive domains (in MCD at least two)	
Criterion C	specifies the difference between PROBABLE and POSSIBLE AD etiology	
	Major Cognitive Disorder: ***Probable Alzheimer's Disease*** *is diagnosed if either of the following is present, otherwise,* ***Possible Alzheimer's Disease*** *should be diagnosed:* *-There is evidence of a causative Alzheimer's Disease genetic mutation from family or genetic testing,* *-All three conditions are met* *a)Clear evidence of decline in memory and learning in one cognitive domain;* *b)Steadily progress with gradual decline in condition;* *c)No evidence of mixed aetiology (absence of other neurodegenerative or cerebrovascular disease, or other neurological, mental, or systemic disease or condition likely contributing to cognitive decline).*	*mild Cognitive Disorder:* ***Probable Alzheimer's Disease*** *is diagnosed when in presence of a causative AD genetic mutation from either genetic testing or family history.* ***Possible Alzheimer's Disease*** *-There is NO evidence of a causative AD genetic mutation from either genetic testing or family history,* *-All three conditions are met:* *a)Clear evidence of decline in memory and learning;* *b)Steadily progressive, gradual decline in cognition, without extended plateaus;* *c)No evidence of mixed aetiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline)*
Criterion D	states that the NCD must NOT have another etiology beyond Alzheimer, this is, the condition must not be better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance or another mental, neurological or systemic disorder.	

Table 3 - AD diagnose criteria (American Psychiatric Association - DSM-5 Task Force, 2013, p. 611)

2.1.1

Diagnostic Markers & Biological evidences

On a biological level, structures most affected by Alzheimer's Disease include the brain's neocortex and hippocampus.
In early onset cases, genetic testing is possible in one of the known causative AD gene[i], but the definitive diagnosis comes from fulfillment of the clinical criteria described above, plus evidence of histologic post-mortem analysis (Mayeux and Sano 1999); (Perl 2010); (Ballard, Gauthier et al. 2011).

Often times, however, clinicians have to cope with availability and validity issues for many of the biomarkers of the disease, making cerebral biopsy the only widely accepted method to diagnose definite AD. On these patients' cerebral biopsy, cortical atrophy is observed, as well as B amyloid deposition in senile plaques and also intracellular formation of neurofibrilary tangles with abnormal phosphorilated form of a microtubule associated protein[ii] at the level of the limbic region and the parietal-temporal cortex with concomitant loss of neuronal synapses and pyramidal neurons (Francis, Palmer et al. 1999); (Perl 2010); (Ballard, Gauthier et al. 2011); (American Psychiatric Association - DSM-5 Task Force 2013).

In late onset cases, besides the build-up of Beta amyloid protein, de la Torre (2004) suggest cerebral hypo-perfusion as a possible mechanism for neuronal degenerescence.

According to the NICE[iii] clinical guideline 42 on the subject of Dementia, health care staff should firstly start by investigate basic hematology as well as biochemistry, thyroid function, vitamin B12 serum and folate levels, after what, the focus should turn to patients anamnesis, physical examination, evaluation of current medication (screening for drugs that might impact on the patients cognitive function), and of course, Cognitive and Mental Examination. Concerning this later recommendation, a set of neurocognitive tests are

i (B) beta Amyloid Percursor Protein (APP) gene, on chromosome 21

ii Tau protein

iii National Institute for Health and Clinical Excellence

suggested to be performed on the patient, namely the Mini Mental State Examination (MMSE), 6-Item Cognitive Impairment Test (6-CIT), General Practitioner Assessment of Cognition (GPCOG) and 7- Minute Screen test, taking into account factors like educational level and skills psychiatric illness, physical and neurological problems, language and sensory impairment. Also in the case of individuals with learning disabilities, alternative tests are proposed, like the Cambridge Cognitive Examination (CAMCOG), the Modified Cambridge Examination for Mental Disorders of the Elderly (CAMDEX), the Dementia Questionnaire for Mentally Retarded Persons (DMR) or the Dementia Scale for Down Syndrome (DSDS) (also useful in people without Down's syndrome).
For further definition of the subtype of dementia, NICE guidelines recommendations include the NINCDS-ARDA criteria, ICD-10 or DSM-IV, already addressed above (National Institute for Health and Care Excellence 2006).

2.1.2

Risk and prognostic factors

Several aspects may be pointed out as possibly increasing the likelihood of developing AD, among which: sociodemographic factors; familial and genetic factors; cognitive function (as in education and intelligence); medical and pharmacological history; and of course, life-style habits (Ames, Burns et al. 2005). Among these, family history of dementia, (specially when the disease occurs on first degree relatives), head injury and specially age seem to be the strongest predictors (Gentleman and Roberts 1992); (Ames, Burns et al. 2005).

Age is, in fact, quoted as the strongest risk factor in Alzheimer's Disease. This is probably one of the main reasons for its common late detection, since it is considered normal to somehow loose pristine memory function as one grow old. But the fact remains that the process of aging itself is not cause for dementia, nor for that matter, AD, because the regular decrease in neurological and psychomotor symptoms that normally arouse with the aging process is NOT of sufficient severity to cause dysfunction that disturbs daily activities (Robert L. Kane, Joseph G. Ouslander et al. 1994); (Petersen, Doody et al. 2001); (American Psychiatric Association - DSM-5 Task Force 2013).

To better help general public differentiate Alzheimer evidence signs, from normal

aging signs, the Alzheimer's Association established a list composed of ten warning signs for the early detection of the disease[i] (refer to table 4).

Alzheimer's Disease warning signs	*1-Memory loss that disrupts daily life* *2-Challenges in planning or solving problems* *3-Difficulty completing familiar tasks* *4-Confusion with time or place* *5-Trouble understanding visual images and spatial relationships* *6-New problems with words in speaking or writing* *7-Misplacing things and losing the ability to retrace steps* *8-Decreased or poor judgment* *9-Withdrawal from work or social activities* *10-Changes in mood and personality*

Table 4 - Ten warning signs of AD - adapted from (Alzheimer's Association 2012)

2.1.3

Disease Course and Pharmacological Treatment

As the clinical picture evolves, specific signs of functional impairment gradually increase. Both cognitive deficits as well as psychobehavioural changes poses serious challenges to the patients daily routines, with several dimensions within their life being affected. What often started years before, as a subtle amnesic episode, may result a few years later in an fully dependent human being, oblivious to its surrounding world (ESRO 2014).

General measures as exercise, good nutrition and social interaction are a relative imperative for the recovery of many life threatening diseases, and as was to be expected, so in here, prevention and prophylactic measures have an important role (Ballard, Gauthier et al. 2011).
Besides that, and when defining a therapeutic strategy, one might think of the general picture, which in the case of neurocognitive diseases is a rather complicated task because of the diversity of symptoms that arise during its course - from depression to behavioral problems, an array of symptoms usually demands an array of measures.
Pharmacological treatment in Dementia, Alzheimer's Disease and cognitive impairments therefore, seems limited in the way that there isn't one substance

i as the original

capable of reverting the complex picture of the disease, which usually includes symptoms of agitation, aggression, wandering, depression and apathy (Zec and Burkett 2008).

Concerning solely neurocognitive disorders, several classes of medicines are used to revert the symptoms of the cognitive deficit, namely: nootropics, (stimulant medicines as piracetan); cerebral vasodilators (ergot, papaverin isoxsuprine); calcium channel blockers as nimodipine; N-methyl-D-aspartate receptor antagonists (Memantine) and cholinesterase inhibitors (Goodman 1996); (Sink, Holden et al. 2005); (Birks 2006); (National Institute for Health and Care Excellence 2006); (National Institute for Health and Clinical Excellence 2011).

From these pharmacological classes, one stands out when it comes to Alzheimer's Disease. Aimed specifically at coping with the cognitive symptoms experienced by AD patients, acetylcholinesterase inhibitors (AChEi) are amongst the most widely used drugs in clinical practice, acting by limiting the breakdown of acetylcholine in synaptic clefts, thus increasing cholinergic synaptic transmission, and hence, its concentration on the brain - examples include Donepezil, Rivastigmine, Galantamine (Francis, Palmer et al. 1999); (Birks 2006) (Lanctot, Herrmann et al. 2003); (Trinh, Hoblyn et al. 2003); (National Institute for Health and Care Excellence 2006, National Institute for Health and Clinical Excellence 2011).

Choline acetyltransferase and acetylcholinesterase are both found in high concentration on cholinergic neurons and cholinergic brain synapses.
These enzymes are responsible for the synthesis and respectively the degradation of acetylcholine (ACh), a neurotransmitter with a major indirect influence on memory and on the learning process (Perry, Tomlinson et al. 1978); (Francis, Palmer et al. 1999); (Kaduszkiewicz, Zimmermann et al. 2005).
These medicines act on the basis of neurodegeneration of the basal forebrain, as the reduction of acetylcholine and/or choline acetyltransferase (ChAT), imposes serious impairments on patients memory (Perry, Tomlinson et al. 1978); (Francis, Palmer et al. 1999); (Mayeux and Sano 1999).

"since 2006, literature on new agents for the pharmacological management of AD and other dementias has been characterized by disappointing failures"

(Herrmann, Lanctot et al. 2013)

Increasing cholinergic neurotransmission is therefore a way to revert the cognitive deficit experienced by AD patients, justifying the recent focus of the pharmaceutical industry on the development of this class of drugs. Even so, although pharmacological treatment with AChEIs shows some improvement in neuropsychiatric and functional level of clinical significance, Trinh et al. (2003) consider this benefits to be of modest magnitude in mild to moderate Alzheimer's Disease , furthermore, despite this moderate beneficial effect, discontinuing AChEIs may lead to worsening of symptoms, a situation in which the clinician has to balance the option to continue pharmacological treatment versus the risk of the therapy side effects (Kaduszkiewicz, Zimmermann et al. 2005); (Sink, Holden et al. 2005).

2.2

SCALES AND ASSESSMENT

Effective clinical diagnose of Alzheimer's Disease, requires the usage of neuropsychological tests to measure cognitive, behavioural and functional assessments, according to a prevailing diagnostic criteria[i].

As the disease progresses, the symptoms are gradually manifested with ever higher intensity and developing a suitable instrument capable of differentiating between several types of dementia as well as categorizing the stage within that particular type is a challenging endeavor.
Besides the specificities of validation, reliability and sensitivity criterium, the subjects under evaluation tend to be elderly, with a rather complicated symptomatological picture, which in all, confers upon them characteristics of short cooperation periods, making it hard to develop and administer such a measuring tool. Robert et al. (2010) summarized the ideal characteristics of a multi-domain AD scale for daily medical practice:

1) Easy and quick administration by an experienced clinician; about 10 minutes administration time
2) Reliable and valid for AD

i NINCDS-ARDA, DSM-IV, ICD-10

3) Covering AD relevant areas, like cognition; activities of daily living; behaviour; communication and social interaction and quality of life
4) Applicable to all AD severity stages (with minimal floor and ceiling effects)
5) Useful for monitoring disease progression in clinical practice
6) Sensitive to measure therapy effects

adapted from (Robert, Ferris et al. 2010)

Assessment tools used to evaluate the outcome of a given therapeutical measure in the case of Probable or Possible Alzheimer's Disease, include an array of cognitive and functional tests with two of the most commonly used being the Mini Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale - cognitive sub-scale (ADAS-cog) (Folstein, Folstein et al. 1975); (Birks 2006); (National Institute for Health and Care Excellence 2006); (National Institute for Health and Clinical Excellence 2011); (Robert, Ferris et al. 2010); (Bossers, van der Woude et al. 2012).

In a recent literature review of 89 RCT[i]s, with the objective to recommend a group of neuropsychological tests to use in clinical trials for cognition assessment in older patients with dementia, Bossers et al. (2012) refer the Severe Impairment Battery (SIB), Mini Mental State Examination (MMSE) and Alzheimer Disease Assessment Scale (ADAS-cog) as tests commonly used to evaluate global cognition.
From these later, MMSE and ADAS-cog where the most often administered for this purpose, with the majority of interventions (84%) being made on Alzheimer's Disease diagnosed patients, independently of the type of intervention (pharmacological, acupuncture, exercise, etc.).
In terms of reliability, these same authors conclude that MMSE is both reliable and valid in dementia patients, although with a floor effect in severe dementia (Bossers, van der Woude et al. 2012).

2.2.1

Tests Description

MMSE - Mini Mental State Evaluation
The Mini Mental State Evaluation test is a simplified and scored form of cognitive

i Randomized Control Trial(s)

mental status evaluation, analyzing cognition in seven different categories, namely: Orientation; Immediate Recall (Registration); Attention, Calculation; Delayed Recall, Language and Visual Construction.

It encompasses a 30 point scale, comprising eleven questions aimed specifically at the evaluation of the severity of the cognitive impairment. Although there is not a specific time limit to its completion, it usually doesn't take more than 5-10 minutes to administer.
The test is divided into two sections - the first part requires only vocal answers and covers orientation, memory and attention, while a second part tests the ability to name, follow verbal and written commands, spontaneously write a sentence and copy a geometrical form (Folstein, Folstein et al. 1975); (Chaves ML 2011); (Bossers, van der Woude et al. 2012).

Folstein (1975) proved its validity and reliability as an initial and serial measuring tool, allowing the follow up of cognitive function over time, with or without treatment. However, Bowie et al. (1999), when assessing MMSE reliability on detecting small changes in cognitive function, has drawn a different conclusion, stating that the test is not powerful enough to detect score differences, when changes in cognitive function are small, allegation which is also supported by the Wessex Institute for Health Research and Development on the its paper on the Clinical and Cost Effectiveness of Donepezil, Rivastigmine and Galantamine for Alzheimer's Disease (Clegg, Bryant et al. 2002).

The 30 point MMSE scale allows the differentiation of the degree of severity of the disease, where an increase in numeric value represents an improvement in cognitive function (table 5).

Mini Mental State Examination	
Item Description and valuation	Score
Orientation (10 points) *Immediate Recall (Registration) (3 points)* *Attention and Calculation (5 points)* *Delayed Recall (3 points)* *Language (3 points)* *Visual Construction (3 points)* *Follow Instructions (3 points)*	*Mild AD: MMSE 21 to 26* *Moderate AD: MMSE 10 to 20* *Moderately severe AD: MMSE 10 to 14* *Severe AD: MMSE less than 10.*

Table 5 - Mini Mental State Examination description and score

In the scope of the present article, we will use the MMSE (Mini Mental State Exam) as a cognitive screening instrument. The reasons behind this choice are the relative easy of usage, its broadly acceptance as an instrument for the measure of cognitive loss (Chaves ML 2011); (Bossers, van der Woude et al. 2012).

Alzheimer's Disease Assessment Scale (ADAS)

Alzheimer's Disease Assessment Scale (ADAS) was developed by Rosen et al. (1984), in order to evaluate the severity of both cognitive and non cognitive dysfunctions of individuals with AD. Birks (2006) and Robert (2010) mention the fact that this is actually the preferred clinical trials cognitive test, when assessing therapeutical efficacy in cognition within AD patients.

The global scale encompasses 40 items, 11 of them belonging to the assessment of cognitive function.

This 11 items psychometric scale (see to table 6), tests memory, orientation, language, attention, reasoning and following instructions abilities (Peña-Casanova 1997).

Point evaluation range from 0 - No Impairment, to 70 - Very Severe Impairment, where a decrease in the score means improvement in cognitive state. The test usually takes about 30 to 45 minutes to administer and it seems to be specially suited for patients suffering from moderate stage of the disease.

Alzheimer's Disease Assessment Scale - cognitive subscale	
Items description and point valuation	*Spoken Language Ability (0-5)* *Comprehension of Spoken Language (0-5)* *Recall of Test Instructions (0-5)* *Word Finding Difficulty (0-5)* *Following Commands (0-5)* *Naming Object (0-5)* *Construction Drawing (0- 5)* *Ideational Praxis (0-5)* *Orientation (0-8)* *Word Recall (0-10)* *Word Recognition (0-12)*

Table 6 - ADAS-cog, cognitive domain valuation

The challenges posed by both MMSE and ADAS-cog, are usually related to their lack of sensitivity on early stages of the disease, and specifically when it comes to ADAS-cog, the fact that it does not include items for dictation, abstraction, calculation and problem solving (Peña-Casanova 1997); (Robert, Ferris et al. 2010).

Clock Drawing Test

Despite not being a definite indicator of AD and more suited to access executive functioning, the Clock Drawing Test aids researchers and clinicians assess the degree of dementia severity (Bossers, van der Woude et al. 2012).

The test involves complex and simultaneous cognitive, motor and perceptual abilities for successful completion. Different investigators use divergent forms of administration, most of them involving asking the patients to draw the face of a clock in a piece of paper. The patient is later asked to fill in the numbers and the arms of the clock, so that they represent "ten minutes after eleven" (Shulman 2000); (Fuzikawa, Uchôa et al. 2003).

Various methods of scoring are described in literature, and overall best scores result from correctly drawing and spacing the numbers as well as placing the clock hands at the asked time (Brodaty and Moore 1997). Shulman (2000) proposed a simple method for scoring - classifying errors from 1 to 5 -, where better performances are positively correlated with higher punctuations.

The advantages of using the clock drawing test remain the simplicity of its administration, its low cost, the fact that it doesn't need any specific materials, as well as its high levels of sensitivity and specificity as a cognitive screening instrument. When used in combination with MMSE, the combined sensitivity and specificity of both tests for differentiating between patients with AD, Mild Cognitive Impairment and Healthy Controls is superior to MMSE, when it is used alone, and similar to ADAS-cog, with the benefits of an easier and faster administration (Shulman 2000); (Fuzikawa, Uchôa et al. 2003); (Kato, Narumoto et al. 2013).

Dementia Rating Scale

Another practical prominent scale for usage on the evaluation of cognitive capacity of subjects with neurological impairments is the Dementia Rating Scale (DRS) (Jurico, Leitten et al. 2011).

The DRS[i] is both useful in the early diagnose of dementia as also in stage classification. It encompasses 36 chores and 32 stimuli, organized on the course of five sub scales, allowing the collection of information on specific cognitive abilities namely: Attention; Initiation/Perseverance; Construction; Conceptualization; Memory.

One of the advantage of this scale is the progressive (or hierarchic) rating system, according to which more difficult tasks are presented at first within each sub scale, meaning that on successful completion of any of these first tasks, the surveyed subject gets credit for tasks to come that belong to the same group, allowing them to move forward to the following group of tasks.
This procedure, in all, allows reduction of the test completion time to 10 to 15 minutes in patients with normal cognitive function, (the test takes approximately 30 to 45 minutes to administer in moderately impaired subjects).
Another asset in favor of this scale in the scope of the present study, is the fact that it is currently validated for usage in the portuguese population and also the strong evidence of the test's reliability and internal consistency on AD patients (Vitaliano, Breen et al. 1984); (Matteau, Dupré et al. 2011).

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i Dementia Rating Scale

2.2.2

Pharmacological Treatment and Neuropsychological Scales

On a systematic review of randomized clinical trials, 22 publications from a total of 412 references met the inclusion criteria for the evaluation of possible scientific evidence of the clinical benefits of AChEIs[i] (Donepezil, Galantamine and Rivastigmine) in AD patients. Of these trials, 14 publications used ADAS-cog[ii] as the psychometric test to measure the outcome in terms of cognitive function, from which 12 yielded significative differences when comparing the usage of AChEIs with placebo.
In terms of the improvement on the measuring tool (ADAS-cog), mean differences ranged from 1,5 points to 3,9 points (Kaduszkiewicz, Zimmermann et al. 2005).

Birks et al. (2009), reviewed the effects of Rivastigmine on AD, analyzing 9 unconfounded, double-blinded, randomized studies, where the drug was administered to a total of 4775 AD diagnosed patients for more than two weeks, with initial MMSE[iii] scores from 10 to 26.
Results of cognitive function showed improvements for Rivastigmine dosages between 6 to 12mg daily, where MMSE increased by 0,8 points and ADAS-Cog decreased by 2,1 points. On groups receiving 1 to 4mg daily, improvements were also felt, although they where not as strong, as those obtained with higher dosages.
These results are inline with those obtained earlier by Rosler, et al. (1999), where patients receiving the same Rivastigmine dosage (6 to 12mg/daily), over a 26 week period, improved on ADAS cognitive sub-scale by a mean of 1,2 point score.

Another review by Birks (2006) included a total of 7298 patients distributed through 13 trials, all multi-centered, randomized, double-blinded and parallel. Patients were diagnosed with Mild AD in 1 trial (mean MMSE 24); Mild to Moderate AD in 10 trials (MMSE 17 to 20); and Severe AD in 2 trials (MMSE 12 and 14 respectively).

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i Acetyl Cholinesterase Inhibitor

ii Alzheimer's Disease Assessment Scale - cognitive sub-scale

iii Mini Mental State Examination

From the total number of patients, 2228 received Donepezil, 2267 Galantamine and 2803 Rivastigmine.

The patients were screened for Global assessment, Cognitive Function, Activities of Daily Living and Behavioural Disturbance, yielding the following results concerning Cognitive Function after approximately 6 months treatment:

-10 studies contributed to ADAS-cog meta-analysis (3 concerning treatment with Donepezil, other 3 with Galantamine, and the remaining 4 with Rivastigmine). The treatment effect revealed a decrease from 1,4 and 3,9 points on ADAS-cog scale, from which Rivastigmine showed more variation both in treatment as in placebo group, effect not felt with the any of the other medicines.

-9 studies contributed to MMSE meta-analysis (5 concerning treatment with Donepezil and 4 Rivastigmine), with treatment effect ranging between 0,65 and 1,8 points in eight of the trials.

3

TRADITIONAL CHINESE MEDICINE

3.1

BACKGROUND

The World Health Organization (2010) recognizes *Traditional Chinese Medicine* (TCM) as a variety of therapies and medicinal practices employed in China for the last two millennia, developed from clinical experience and recorded in classical ancient scripts. The first known book on the subject of Chinese Medicine, the Huangdi Neijing - the *Yellow Emperor Cannon of Internal Medicine* -, dates back to the years 475–22BC and documents human structure and physiology as well as disease pathophysiology and treatment procedures.

Nowadays, higher education on TCM is available, not restricted to universities and colleges throughout China, but also in several other developed countries (World Health Organization 2010). More than ever, it is crucial to establish the bridge between both knowledges, a kind of “West meet East”, allowing the incorporation to each of these medicine concepts, the best both have to offer.

Chinese medicine concepts stand on the basis of Confucianism, Daoism and Taoist philosophy to explain its holistic medical reasoning concept, according to which the human being and its surrounding environment are in constant equilibrium. Understanding the “laws” of nature is therefore paramount to interpret how living organisms respond and reflect the macrocosmos (or the environment). Within this equation, metabolism, homeostasis and adaptation are the basis for life, and this point of view of the human body as an open system, considers all of its structures and components as interrelated subsystems establishing functional relations, so that a rather complex dynamic balance must be obtained to achieve a disease free organism.

Due to political and cultural restrains, both inbound and outbound information in and from ancient China was scarce, resulting in part of this knowledge being lost throughout time, as well as rather difficult to interpret in light of an western educated mind. Naturally, with all the advances observed in the last centuries in the fields of medicine, physiology, pathophysiology and anatomy, western medicine concept grew apart this ancient oriental knowledge. Nevertheless, along with the continuous development of Tradicional Chinese Medicine, several

schools and scholars have been making an effort to recover information and systematize it, seeking a modern and more rational interpretation of specific intricate TCM concepts, to find its equivalency and usefulness to Western Medicine (Porkert, Hempen et al. 1999); (Teppone and Avakyan 2009); (Greten 2011, Greten 2012); (Tsui 2013).

An enlarged understanding of TCM is out of the scope of the present study, however, several theories on the basis of Tradicional Chinese Medicine will be addressed, namely the *Theory of Yin and Yang*, *Theory of the Five Movements (Phases)*, the *Theory of Qi and the Conduit System*.

3.1.1

TCM Definition

According to the Heidelberg School of Chinese Medicine (Greten 2011), Traditional Chinese Medicine is a system of findings and sensations, designed to evaluate the functional vegetative state of the body, further treated by an array of tools such as Chinese Dietetics, Psychosomatic TCM, TuiNa Massage, Chinese Phytopharmacology, QiGong and of course the most known of all the techniques within TCM, Acupuncture.

Porkert et al. (1999), defines health in the scope of Chinese Medicine, as the capacity to maintain orthopathy[i] - *"the tendency or the capacity of an individual to maintain integrity (…) well-balanced physiological, intellectual, emotional functions"*.
This later state is, however, challenged by several factors, impacting the system as a hole, or in respect to its particular features. In a sense, in the scope of TCM's theory, restoring one's health translates to restoration or normalization of these imbalances (Teppone and Avakyan 2009).

i Within the scope of the scientific vegetative Heidelberg Model of Chinese Medicine, a hole new hermeneutic system was developed in order to translate TCM concepts in light of medical western thinking. *Orthopathy* symbolizes literally "straight running functions"

3.1.2

Theory of Yin and Yang

"All things connote the Yin and yang. The Yin and Yang keep acting upon each other. And thus things keep changing and unifying themselves"
(Roberts 2004)

Yin and Yang are probably amongst the most world widely spread concepts of Chinese culture. They relate to each other like both sides of one same coin - it is not possible to explain one without the other.

Chonghuo (1993) postulates the following, regarding Yin and Yang concepts:

Postulate 1
Yin and Yang Contradiction
Every phenomenon of nature, has, at the same time, two opposites;

Postulate 2
Yin and Yang are Complementary
Each of the opposites exists as long as there is the other. There is no Yin without Yang, and vice-versa. When one them is not present, there is no possibility for life to exist;

Postulate 3
Growth and Decline Relation of Yin and Yang
Change and movement is the essence of both Yin and Yang. If one grows, the other retracts in order to obtain a dynamic equilibrium. An example are the changes seen in environmental seasons - from Spring to Summer, Yang heat increases, while Yin cold decreases. Also in living organisms, general physiologic function (Yang) increases through consumption of nutrition (Yin). This balance is always compensated to the point that If one of them rises or decreases too rapidly the balance is broken and disease might arise;

Postulate 4
Yin and Yang transmutation
By which Yin becomes Yang and Yang becomes Yin.

There is not one, but several approximate metaphorical meanings for these concepts. In the spectrum of both Chinese Medicine and Chinese Culture, the terms are applied to describe functional relations:

-Where the Yang is pictorially represented by the sunnier side of a mountain, the Yin will be

illustrated by the shadier side of that same mountain;
-The Yang represents a state of higher energy when compared to its counterpart the Yin, with lesser energy;
-When the Yang represents expansion the Yin will be contraction;
-The Yang, relates to anything in the state of "more on the outside" compared to the Yin, "more on the inside";
-The Yang finds parallelism with the function, but that function arises from the Yin, represented by the structure;
-The Yang is a state of more disperse energy, and the Yin a state where that same energy is more dense;
-The Yin is represented by Winter whereas the Yang is the Summer, or the Yang might be Spring, compared to Autumn that is Yin;
-...and so forth...

In the same way that the relation is found in nature and all things, likewise every body part and structures exhibit Yin and Yang aspects. The anterior part of the body is Yin in relation to the posterior that is Yang, the upper part is Yang in relation to the lower part which is considered Yin. Organs also fall into this type of categorization - for this matter, TCM established organ pairs that are functionally related in both cyclic and in a counter-regulatory way.

Another manner to describe this terms is by the usage of numbers. The Chinese Monad is the perfect example of this statement. Together, Yin and Yang describe a relationship between apparent opposite sets that counterbalance each other, and translating them into a binary mathematical comparison system, every aspect of life can be described using different combinations (Porkert, Hempen et al. 1999); (Teppone and Avakyan 2009).

The understanding of the Yin and Yang theory is therefore fundamental to the understanding of Tradicional Chinese Medicine itself. Restoring health in the view of TCM, relies on the equilibrium of these counterparts (Cheung 2011); (Tsui 2013); (Zhang and Wang 2014).

3.1.3

The Theory of the Five Movements (Phases)

The basis of TCM, holds that there is a parallelism between nature and living organisms, stating that they exhibit similar rhythmical changes and functioning.

As the environment is cyclically divided in four seasons, the same relation can be seen in living organisms. TCM considers four basic movements, often known as *elements*: **Wood** (related to Spring); **Fire** (related to Summer); **Metal** (related to Autumn); **Water** (related to Winter) and a special fifth with very specific functions - the **Earth**.
According to Tsui, (2013) this model of the five movements is explainable in light of sequential functional restrains and promotions suffered by each movement in the continuum.

The vegetative Heidelberg Model of Chinese Medicine relies on a simplified concept of cybernetic regulation, where vegetative functions are continuously being expressed in a circular style, resulting in a likewise sinus curve (figure 1) (Greten 2011).

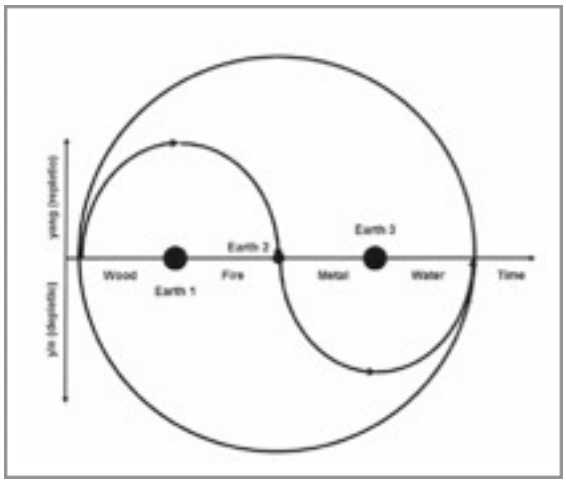

Figure 1 - Sinus wave as basis for theoretical approach to the Heidelberg Model of Chinese Medicine

On this mathematical/vectorial pictogram, all of the body's regulatory function are expressed as a relation to a baseline value representing the homeostasis threshold (the horizontal line).
The part of the graphic above the threshold represents several Yang aspects of regulation and the lower part, Yin aspects of regulation. Each quarter of a cycle represents a phase and at each inversion point, a new phase arises from the later.

With this model, Greten (2011, 2012) circumvents the misleading use of the term *element*, defining instead the *phase* - a cybernetic or regulatory term, part of a circular process, symbolizing a functional vegetative tendency which is

manifested in a specific body part by means of clinically relevant signs and symptoms named orbs[i].

Like Spring turns into Summer, which in turn gives place to Autumn and this later to Winter, this natural movement of seasons is illustrated by this regulatory model, where the phase **Wood** transitions to the phase **Fire**, this one into **Metal** and the later into **Water**. To this, the phase **Earth** is added, representing the dow-regulation or up-regulating vector that powers the phase transitions, resulting in a total of eight phase transitions (Wood-Earth-Fire-Earth-Metal-Earth-Water-Earth-Wood).

Furthermore, each phase encompasses two organs or Orbs (exception made to the phase Fire which was later on split in four orbs for scientific systematization reasons), each of them presenting either a Yin or Yang predominant aspect (table 7).

Phase	Yin orb	Associated Yin Organ	Yang orb	Associated Yang Organ
Wood	*Hepatic Orb*	*Liver*	*Felleal Orb*	*Gall Bladder*
Fire	*Cardial Orb*	*Heart*	*Tenueintestinal Orb*	*Small Intestine*
Fire (2)	*Pericardiac Orb*	*x*	*Tricaloric Orb*	*x*
Earth	*Lienal Orb*	*Spleen & Pancreas*	*Stomachal Orb*	*Stomach*
Metal	*Pulmunal Orb*	*Lung*	*Crassintestinal Orb*	*Large Intestine*
Water	*Renal Orb*	*Kidney*	*Vesical Orb*	*Bladder*

Table 7 - Yin and Yang Orbs according to the respective phase

According to Gretens's (2012) model of vegetative regulation, during the Yang phases (**Wood** and **Fire**), sympathetic nervous system prevails while on Yin phases (**Metal** and **Water**), parasympathetic stimuli is more expressed. Phases **Wood** and **Fire** are characterized a hyper-tone and hyper-dynamic vegetative state, when compared to **Metal** and **Water**, that are respectively more hypotonic and hypo-dynamic (figure 2).

i This term is part of the Heidelberg Model hermeneutics. Although its definition might exhibit some similarities with an actual organ in western medicine, an orb is comparable to an organ pattern, or to the signs manifested by that organ

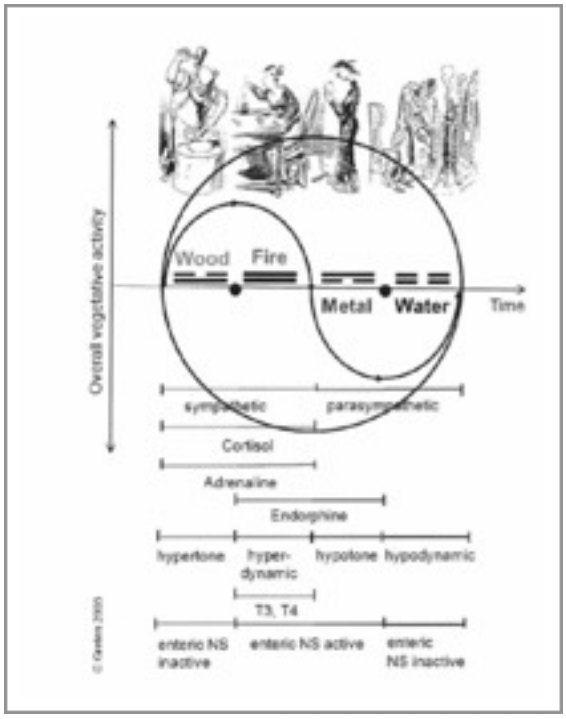

Figure 2 - Sympathetic and Parasympathetic states of the HMCH (Greten 2011)

Consequently, each of the phases presents different specificities within this vegetative regulatory system of the living organism. The phase **Wood** is related to the creation of potential. It is associated with ascending movements like the increase of excitation, and it is followed by the phase **Fire**, where the function reaches its peak and initiates its down-regulatory movement. Greten describes **Fire** as the phase where transformation of potential into function occurs. The following phase, **Metal**, is described as functional relaxation. With its prevailing Yin aspects, there is a relative lack of energy, and by action of the orbs Pulmunar and Crassintestinal the energy "descends" and is distributed throughout the body. Finally, the phase **Water** is the regenerative phase of the cycle. Within this phase, all functions reach their lower in terms of energy, and initiate their ascend. This is why the Renal Orb is considered to be the storage house of the essence, the source of energy.

The phase **Earth** represents the equilibrium and the power of regulation. The movement of the phases is possible because of the Earth's capacity to up or down regulate. This is to say, for instance, that when the maximum Yang is reached in **Wood**, the descending vector **Earth**, represented by the Stomachal Orb,Xue inverts the curve, giving birth to the phase **Fire**, and on the maximum of Yin in **Metal**, the ascending vector of the **Earth** phase, the Lienal Orb, brings the energy up, "keeping the wheel turning" (Greten 2011).

3.1.4

Theory of Qi and the Conduit System

Porket et al. (1999) defines Qi as an immaterial energy with a qualification and a direction, whereas an auxiliary vegetative definition is brought by Greten (2012), stating that Qi represents the "*vegetative capacity of an organ or tissue to function, which may cause a sensation of tearing, pressure or flow*".
Special qualifications of Qi point to its diverse functions within the system of TCM. Original Qi (or Yuan Qi), is the source of all energy, represents the essence stored in the Renal orb, the basis of all Yin and Yang energies of the body and it is dispersed by the Tricaloric Orb, propelling the organs functional activity and assisting the production of Xue[i]. Another example is defensive Qi, (or Wei Qi) - a particular form of Qi located outside the conduit network, believed to ward off exogenous pathogens.

Teppone & Avakyan (2009) compare Qi to an universal qualitative measuring unit, something that physicians could measure, regulate and manipulate in order to achieve different states (which makes sense, since despite that there is no 5Qi ou 6Qi, TCM tends to qualify divergent states as having more Qi or less Qi). From this later statement, inference can also be made in order of the condition of excess or deficiency, reflecting respectively, status of high or low activity.

According to TCM theory, this energy flows within the body through specific pathways called "conduits". Greten (2012) further defines conduit[ii] as a *"connection of a group of points with effect on the clinical signs of an orb, believed to serve as a conduit for the flow of Qi and Xue"*.
The conduit system consists of different pathways, where several connections exist between specific body regions, namely intracellular spaces or cavities, by which, due to their biological, morphological and functional complexity, interactions to the exterior environment occur (Tsui 2013), which is actually the basis for acupuncture. In a general sense, imbalances on this flow of Qi might result in diverse pathological outcomes and acupuncture is therefore used as a means to correct them by choosing specific acupoints within these conduits, that

i Within the HMCM, Xue refers to the functional capacity bounded to body fluids, with functions to nurture, moisten, bring warmth and Qi to the tissues. It is directly related to effects of microcirculation, which in western medicine is similar concept to the blood.

ii Within International nomenclature, the meridian

in turn will develop specific regulatory actions.

Tsui (2013) states that the sheer nature of Qi is also important when it comes to differentiate the concepts of health and disease. The key aspect here, is once again equilibrium. Resorting to an example, heat and cold within the body describe intensity of heat production and therefore also the state of Qi. When exothermic reactions exceeds the normality threshold, TCM doctors may think of a manifesting disease with heat symptoms requiring "*cleaning the heat".* The opposite is also plausible - when presented with an exacerbated endothermic reaction, the physician may be lead to consider an affection by cold, or a cold disease, requiring warming therapy.
On a disease free organism, thus, the Qi has both the *correct direction* and it is *strong in nature*, thus allowing Xue and body fluids[i] to effectively nourish the tissues[ii]. When a patient exhibits a *healthy* Qi, functions are exerted by the organs without distress, and there is strong resistance to exogenous pathogenic agents.

i In classical TCM theory, the body fluids have the designation of Jinye

ii We will not approach at this instance the relation between Qi and Xue. It is sufficient for now the understanding that if Qi is healthy, this will contribute decisively to the production of "healthy" Xue

3.2

TCM DIAGNOSE

As in Western Medicine, TCM diagnose relies on the gathering of clinical information from inspection, palpation, auscultation, olfaction and inquiring. Together, all this information is then compiled to attain the Zheng concept, a fundamental notion in Chinese Medicine reflecting an organized pattern of all clinical manifestations, allowing the differentiation of specific targeted medical approaches. In western terminology, one might compare it to the classification of a syndrome (Su, Lu et al. 2012).

Concerning the diagnosis, there are four main mechanisms leading to imbalances, as principles of disease (Greten 2012):
Excess of an agent[i] - the pathogenic factor eliciting the imbalance;
Problems of transition - functional vegetative regulation occurs in a cyclic way and a phase expresses a part of this cycle - when transition does not occur, signs and symptoms of dysregulation are elicited and the disease is manifested;
Imbalance of antagonizing phases - as the phases are upward and downward "vectors" within this model of vegetative regulation, they counterbalance each other - when this balance is not present, there is dysregulation, and hence, disease;
Yin deficiency - if there is a Yin deficiency, this means that there is a structural problem. In western terms, there is not enough cell apparatus to surpass the disease.

Greten (2012) systematized the process of diagnosis into four hierarchical important stages explained bellow: Constitution, Agent, Orb and Guiding Criteria (figure 3).

The first of these steps corresponds to the evaluation of the **CONSTITUTION**, which put simply, is the tendency to predominantly express a specific set of signs, revealed in the individual phenotype. The analysis of the constitution leads the TCM doctor to generate initial assumptions about the response of the patient subjected to different conditions.

i An agent is any entity capable of eliciting a disease

Resorting to an example, the therapist usually accounts for telltale signs, evidences like the clenching of the fist, the tone of the voice, the expressivity of the eyes or the movement of the limbs. These observations are partly common sense, but for instance, if the patient's voice is low, like weeping, and he or she present hanging shoulders, this may lead to the assumption of a relative lack of energy and feeble constitution.

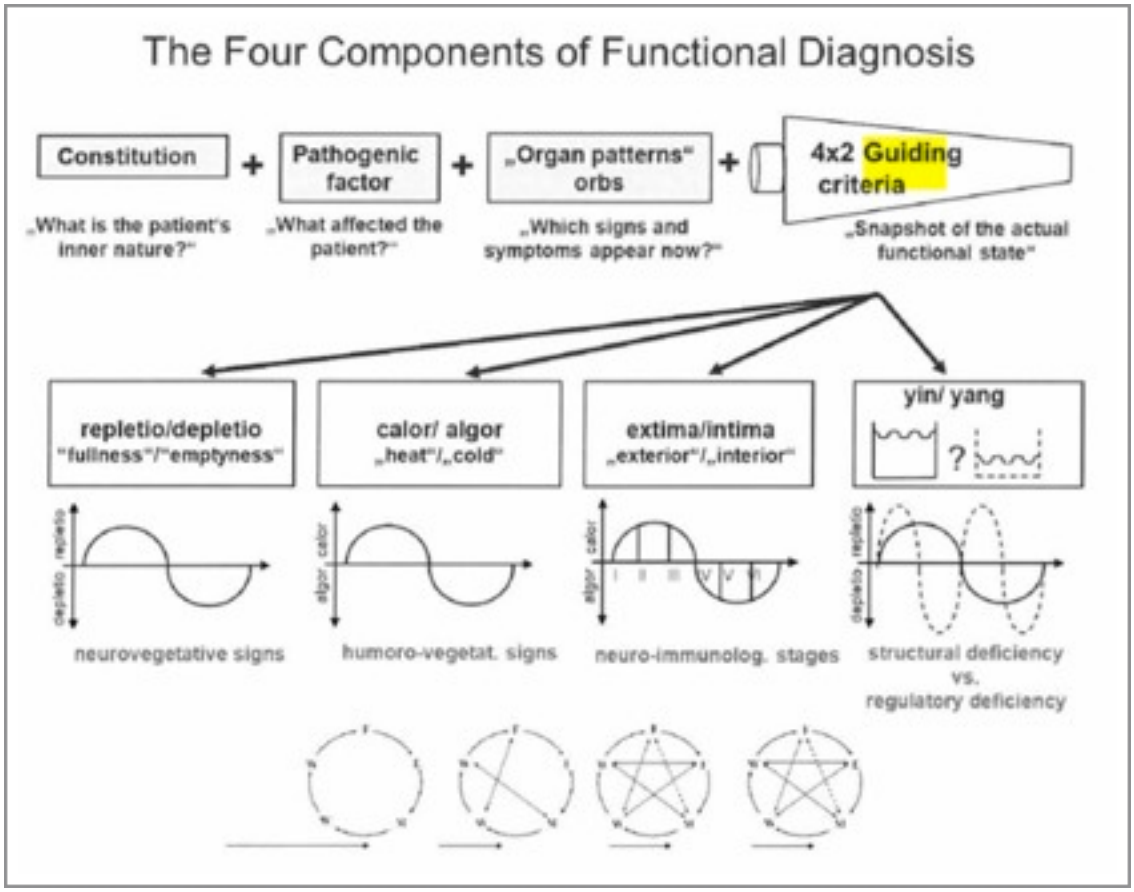

Figure 3 - Functional Diagnose according to the HMCM (Greten 2012)

The second part of the diagnosis is the definition of the **AGENT**, which translates to the pathological vector eliciting the imbalance, on the etiological origin of the disease.

Agents are categorized as External, Internal and Neutral:

E*xternal Agents* find parallelism with environmental conditions experienced by the patient:

Algor[i] *- symbolizing the effects on the body resulting from being exposed to cold;*

Calor - symbolizing the effects on the body resulting from being exposed to heat;

Humor - symbolizing the effects on the body resulting from being exposed to a damp (humid) environment;

Ariditas - symbolizing the effects on the body resulting from being exposed to a dry environment;

Ventus - symbolizing the effects on the body resulting from being exposed to a draught of air.

Internal Agents, generally refer to exacerbated emotions

Ira - or the over expression of anger;

Voluptas - or the expression of uncontrollable over excitement;

Cogitatio - or the feeling of over thinking;

Maeror - or the feeling of grief and sadness;

Timor - expressing frightfulness.

Neutral Agents refer to substances like toxics, harmful medicines, virus or bacteria.

In order to further exemplify the concept of *Agent,* when referring to *cold disease* or *cold attack*, TCM clinicians are in fact symbolizing the resulting effects in terms of the body physiology, particularly when it comes to microcirculation. Being exposed to Algor (or environmental cold), will develop a physiological reaction that in time reduces the Xue content over the body surface. This diminished microcirculation is later on responsible for a specific set of clinically significant signs identified by the physician, called an orb.

The third part of the diagnosis compels the identification of the affected **ORB** or orbs - the observation of clinical relevant signs and symptoms exhibited by a certain body region, representing the manifestation of a phase.

Finally, the last part of the diagnose is composed of another four distinctive decisions or four **GUIDING CRITERIA**, that should be interpreted in order to understand the underlying mechanisms of the disease. These encompass neuro

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i The magnitude of the importance of the agent Algor led to the development of a diagnostic system of its own called the "Shang Han Lun", or within the HMTCM "The Algor Ladens Theory" reflected on the book "The Treatise on Cold Diseases and Miscellaneous Disorders" (Shang Han Za Bing Lun) dated back to 196–204AD (World Health Organization 2010).
According to the model developed 1.800 years ago, there are "layers" of defense within the body physiology, six to be precise, by which hierarchically the agent cold attacks the body.
A fair pictographic representation might be imagined - six stages (or layers of defense) protect critical organs in the living organisms. Within each stage different qualifications of Qi and Xue are responsible for protecting the organs - Algor, the external agent fights each of these organ pairs, until it reaches the next, more interior, critical organs.
The three first layers are located on the extima, meaning that orbs affected at these levels are closer to the surface of the body (or more yang), and symptoms exhibited will have reflections at these "more superficial" levels (Vesical-Tenueintestinal, Stomachal-Crassintestinal and Felleal-Tricaloric). Within these first three stages one might think of more acute diseases. However, the three last stages deal with Yin organ pairs (Pulmunary-Lienal, Hepatic-Pericardium, Renal-Cardiac), and affections here, usually have a more profound impact, compared to chronic diseases in western medicine (Teppone and Avakyan 2009); (Greten 2012).

and humuro-vegetative signs observed during the course of the disease, namely: Repletio/Depletio; Calor/Algor; Extima/Intima; Yang/Yin (table 8).

Guiding Criteria	Type	Signs
Repletio/ Depletio	*Neurovegetative*	*Signs indicating towards a state of more energy or less energy, or more Qi or less Qi, or excess, or deficiency*
Calor/ Algor	*Humoro-vegetative*	*Reflect a set of signs related to blood perfusion.* *If there is an increase in microcirculation, the patient experiences calor (hot) signs, like thirst, yellowish sparse and concentrated urine, red face completion, among others, as a result of the increase of microcirculation.* *If however, there is a regional lack of microcirculation the patient experiences signs of algor (cold), like pale skin, increased sensitivity to cold, etc..*
Extima/ Intima	*Neuro-imunological*	*Point to the localization of the affected orb.* *Extimal diseases, therefore, affect mainly the outer orbs, eliciting outer organ patterns, likewise inner orbs may also be affected by the agent or the imbalance - in which case the manifestation is called an Intimal disease.* *The presupposition is that outer orbs are more accessible by agents and imbalances, as they are more external, and hence, more vulnerable than inner orbs, and when an pathological imbalance occurs, manifesting signs will generally occur firstly on outer orbs.*
Yin/Yang	*Structural vs Regulatory*	*Wether it is of functional nature - like an exacerbation of a regulatory function - in which case it is considered a Yang disease, or if the disease affects the structural tissue - Yin diseases.*

Table 8 - The Guiding Criteria according to the HMTCM

Restoring *orthopathy*, once again, means reestablishing the *normal* functioning of these vegetative capacities, correcting imbalances in order to maintain homeostasis.

In Alzheimer's Disease, the understanding of which features of the system are impaired, is the basis for the development of an assertive therapeutic strategy.

3.3

ACUPUNCTURE

The first mention to acupuncture and moxibustion in a medical text appeared on the “Inner Classic of the Yellow Emperor” (Huangdi Neijing), dated of 200BC. On this historical ancient script, the course of the major conduits was already detailed, as well as attributed names and description of sensitive points located within these pathways (Porkert, Hempen et al. 1999).
Western civilizations however, took time to embrace the technique. Despite the first description of acupuncture by a western physician having occurred earlier on the 13^{h} century, its adoption in Europe is recorded as started subtly and much later, only on the 17th century.

As previously stated regarding the subject of TCM, also when it comes to acupuncture, some skepticism about its effectiveness still exists in our days, particularly in western countries, where TCM concepts are not as easily understood at the light of scientific rational approaches (World Health Organization 2002); (Kaptchuk 2002).
Over the last decades nonetheless, and particularly due to several scientific advances in acupuncture research, the WHO (2002) concluded that there was sufficient data to support its usage for several medical conditions, and its adoption is spreading amongst many western medicine practitioners (Haake, MüLler et al. 2007); (Lee, Shin et al. 2009); (Cheung 2011); (Zhang, Wu et al. 2014).

3.3.1

Acupuncture Mechanism

The therapeutical approach of Chinese Medicine encompasses the correction of imbalances between Yin and Yang, Qi and the phases. Within this vast picture, acupuncture is applied to reestablish disharmonies via corrective regulatory mechanisms.

The United States Department of Health and Human Services, through its National Centre for Complementary and Alternative Medicine (NCCAM), defines acupuncture as a family of procedures designed to stimulate specific points in the

body, using a variety of techniques (NIH: National Center for Complementary and Alternative Medicine (NCCAM) 2006).
According to Porkert et al. (1999), these points may be classified into three categories:
-points within locations exhibiting is increased sensitivity, in reaction to some local disease, called *ashixue*, used for direct, localized and symptomatic treatment;
-points that due to their precise anatomical topology can be located in any individual, confined to the outside of the conduit system, or *extracardinal foramina*;
-points of precise topological location, that besides therapeutical function, also have diagnostic significance, called *cardinal foramina*.

Each conduit is connected to a specific organ or viscera and as such, a conduit acts as an extension of a specific body part, organ, or region. This explains why external factors may influence inner organs and why disturbances at the body level might be felt in *extimal* layers, namely at those specific acupoints.

Acupuncture therapy is also described by some as a kind of reflexology - a regulatory system based on the fact that reciprocal reflexes exists between the Central Nervous System and different parts of the body forming an reflex arc, according to which, exterior stimuli at given receptors flow through afferent nerves into reflex centers, generating responses via efferent pathways, which would explain acupuncture's neural mechanism (Karavis 1997); (Jin, Jin et al. 2007); (Langevin 2008). Researchers have also focused their attention on acupuncture's mechanism at a humoral level, namely on its capacity to modulate neuro-immune responses and pain (Han 2004); (Ding, Hong et al. 2013). Acupuncture has in fact been proven to modulate the release of humoral factors such as opiate-similar substances and some neurotransmitters, like endorphins and encephalins (Jin, Jin et al. 2007). To this neural and humoral mechanism Greten (2011) adds an energetic mechanism.
In this sense, an acupoint represents a location in which stimulation or de-stimulation may be imposed by the therapist or physician, in order to attain a specific regulatory effect on the body's physiology.

Three distinct mechanisms of acupuncture have been described regarding

nociception: *Peripheral*, *Spinal* and *Supraspinal*.
The *peripheral* mechanism is explained on the basis of an axon reflex, where neuropeptides like substance P and calcitonin gene-related peptide are released from afferent nerves producing local vasodilation, modulating immune responses and assisting healing processes. The *spinal mechanism*, also referred as segmental mechanism, proposes that within tissues that share innervation with a specific spinal chord level, dorsal horn neurons may be inhibited by acupuncture via gate control. Depending on the needling technique, sympathetic or parasympathetic activity is affected[i]. Regarding *supraspinal* mechanism, it refers to the neuronal structures affected by acupuncture, capable of activating descending inhibitory pathways like the Diffuse Noxious Inhibitory Controls (DNIC), neurohormonal responses or beta-endorphin mediated descending pain inhibitory pathways from the hypothalamus (Longbottom 2010).

Placing a needle in a specific acupoint is therefore believed to exert several actions at both local, regional and general levels. A *local* sensory stimulation may result in presence and synthesis of opioids, histamine, substance P, etc., whereas at *regional level*, it might result on the activation of dermatomes via reflex arches and at *general* level, the activation of the brain central mechanism of homeostasis via its autonomic system (Karavis 1997). Practitioners will choose a specific acupoint or an acupoints combination, to achieve the desired effect. Naturally, this statement implies that acupuncture has a regulatory direction, and in fact, according to some, the technique is able to revert physiological functions to a state of normality, although within certain limits - *"if a patient is severely diseased, or suffering from a serious organic disease, it will be very difficult to be cured by acupuncture alone"* (Jin, Jin et al. 2007).

3.3.2

Microsystems Acupuncture

In the last decades, TCM arsenal has been amplified by several investigators and investigations, leading to the development of new models of acupuncture. Based on the discovery of specific reflexive somatotopic fields within human anatomy, Microsystems Acupuncture are the perfect example of this broadening of the

i High-intensity needling may immediately increase sympathetic outflow to tissues supplied by the segment, followed by a decrease in outflow, whereas a low-intensity input could reduce sympathetic outflow in the segment

spectrum of TCM (Hecker and Steveling 2006).

Following the work of the French clinician Paul Nogier on the development of the acupuncture system of the ear, Ralph Alan Dale was the first to introduce the term Microsystems Acupuncture at the 1974 World Symposium on Acupuncture and Chinese Medicine.
According to his definition, MA[i] was a formal expression of the entire's body's Qi in each major anatomical region. Having identified reflex systems in the ear, foot, hand, scalp, nose, iris, teeth, tongue, abdomen, back and every long bone, Dale proposed that each of these areas acted as a regional microcosmos, emulating an holographic anatomical arrangement of the whole body as well as its energies, where neurological, diagnostic and therapeutic reflexes, could serve the purpose of correcting pre diagnosed imbalances.

Bouevitch (2003) alleges that Microsystems of Acupuncture theory follows the principle of fractalization, or similarity. Merely from a physics point-of-view, fractals support scientific explanations of events, not only in the scope of MA, but also in several other Chinese Medicine concepts, such as the pathways of Qi flow (the conduits) and even acupoints. Fractal theory may also contribute to the explanation of conduits as wave formations, analogous to informational exchange systems occurring between the interior of a human body and its external environment.
In a general sense, Acupuncture Microsystems are homeostats - cybernetic models that allow information exchange between *intimal* organs and the *extimal* environment in order to maintain physiological equilibrium (Bouevitch 2003); (Hecker and Steveling 2006).

Similarly to the Fractals theory, another hypothesis for the explanation of these systems comes from biology. The theory of Embryo Containing Information of the Whole Organism (ECIWO) considers the human organism a living mosaic, where each unit contains information of the whole - an inborn embryonic feature where each and every cell is totipotential. According to Schjelderup's (1995) point of view this theory explains bio-holographic systems of acupuncture, such as ear acupuncture or foot reflexology, by which various organs and anatomical parts

i MA - Microsystems Acupuncture

are reflected in smaller areas of a circumscribed part of the body, and a stimuli in one of these prescribed acupoints develops an effect on the predetermined body part or organ.

Popular accepted modern acupuncture microsystems include *Ear Acupuncture*, *Scalp Acupuncture*, *Hand Acupuncture*, among others, all of them sharing the same property of projecting body parts and internal organs within a specific boundary limited section of the skin, a kind of cartographic maps, where special connections between points and correlated organs and systems exists.

Different systems reveal organizational variations: within *Ear Acupuncture*, there is a complete representation of organs with correspondent points and areas; in *Korean Hand Acupuncture*, there is a mini scale representation of channels in a very condensed space (hand); in *Yamamoto's Scalp Acupuncture* we find a 12 point representation of the 12 main channels found in regular acupuncture; in *Oral Acupuncture* the system offers punctual representation of coupled paired channels of the five phases seen in the classic TCM theory (Hecker and Steveling 2006).

Curiously, MA had been already observed in the spectrum of *regular* acupuncture, although not immediately identified as such. In order to illustrate this statement Porkert (1999) stresses the importance of the back SHU[i] points, which represent in fact, the 12 main conduits where the functional activity of the body can be assessed.

Bouevitch (2003) believes that one of the advantage of these systems relies both on their ability to concentrate information in a limited surface and also on the fact that the total number of Microsystems is unlimited, providing huge possibilities of treatment from a single diagnosed condition.

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i These dorsal inductories are special points located on the bladder conduit, where maximal manifestation of activity of the 12 orbs emerge, allowing a functional representation of the whole activity of the body

3.3.2.1

Scalp Acupuncture

Scalp Acupuncture (SA), as already noted in the previous chapter, belongs to the array of Acupuncture Microsystems. According to Scalp Acupuncture theory, treatment zones associated with body anatomy and their related functional capacities are mapped into the scalp.
Needles are inserted within the thin layer of tissue beneath the surface of the skull, to a depth of a maximum of 1/2cun[i] with stimulation occurring in a variety of manners such as pulling/thrusting, twirling or electro-stimulation (Dharmananda and Vickers 2000).

Although Chinese Scalp Acupuncture dates back to early ancient China, the majority of the approaches to this technique were developed only in the mid 20th century, when notions of classic acupuncture and TCM were combined with prominent findings in the field of neurophysiology, neuroanatomy and bio-holographic theory. Albeit classical acupuncture also uses head acupoints, SA is considered a different system of acupuncture whose foundations rely on a specific theory of human body somatotopy.

Initial acupuncture mapping of the scalp is attributed by some to the work of Huang Xuelong in the mid thirties. It is common belief that the physician started by theorizing the concept of the existing relationships between certain areas of the scalp and the cerebral cortex, with results pointing to effective treatment of brain diseases (Dharmananda and Vickers 2000); (Yamamoto 2003).

From the several existing Scalp Acupuncture systems, five are amongst the most known worldwide:
Jiao's Head Acupuncture - based on scalp zones corresponding to motor and sensory locations of the cerebral cortex;
Fang's Scalp Acupuncture - based on superimposed pictures of the spine and the human body [homunculus] in a prone position on the scalp, emphasizing speech and memory centers;
Tang's Head Acupuncture - which combines functions of the cerebral cortex and TCM theory of Zang Fu organs;

i The cun is a measure based on the patients body size and 1/2 cun corresponds to about 0,3 to 0,5 inches in a standard adult

Zang's Treatment - mainly used in nervous and mental diseases;
Zhu's Scalp Acupuncture - introducing the concept of therapeutic lines, based on TCM theory of Zang Fu organs and conduits, where four areas are mapped and needle manipulation is characterized by small amplitude lifting and thrusting, accompanied by massage of the respective body part being treated.

Many of the existing Traditional Scalp Acupuncture systems were focused on the capacity to influence the brain's motor centers and the locations to prick were selected according to the representative area of the actual function developed on the cerebral cortex. It wasn't until the seventies, though, that one of the most popular modern scalp acupuncture systems was developed. Japanese anesthesiologist Yamamoto, took SA to the level of a complete acupuncture system. Yamamoto New Scalp Acupuncture (YNSA) (1989) differs from these later classical systems, because it considers an actual MA[i] somatotope on the skull, where all of the human body is roughly represented along the hairline and thus, the points chosen do not necessarily associate with cortex nerve centres .

The proliferation of diverse MA systems, led, as expected, to an array of different methodologies and several nomenclature schemes. In 1989, the WHO Scientific Group (1991), in view of the progressive increase in acupuncture worldwide adoption, issued a proposal for the international harmonization of acupuncture nomenclature, among which, these Microsystems. Within this proposal, scalp acupuncture channels, where attributed an alphanumeric code - MS# - standing for Micro-System.

Heidelberg Scalp Acupuncture

Following previous explanations, the Heidelberg Scalp Acupuncture (HSA) is a somatotopic Acupuncture Microsystem technique, developed on the basis of correlations between specific skull acupoints (the majority related to the Regens[ii] conduit), physiological functions and anatomical regions.

Special functions are attributed to the Regens conduit, also called *Leading Sinartery*. It is a Yang conduit, originated in the perineum and its primary branch

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i Microsystems Acupuncture

ii Or, the <Governing Vessel> in international TCM nomenclature, one of the twelve extraordinary conduits that has no correspondence to any organ or viscera

ascends through the medial plane of the spine, entering the brain between the occipital and the atlas, at the point Rg16[i] . It then goes further up to the top of the skull, descending from the forehead to the basis of the nose at the philtrum and joining the tendinomuscular conduit of the Stomachal orb. On its secondary, more internal branch, despite having the same starting point - the perineum -, it ascends through an abdominal branch, going directly to the heart, then to the brain through the throat and finally to the centre of the eye (Porkert, Hempen et al. 1999); (Greten 2011, Greten 2012). This conduit is also connected to the Renal orb through the *reticulares*[ii] system, exerting great influence over the body's vital energy, or Qi primum.
Stressing its importance as means to correct physiological imbalances, by resorting to this conduit, TCM physicians *bring up* energies from the Renal orb to the surface. The Renal orb and its counterpart, the Cardial orb, are of special importance when it comes to neurological diseases, and this fact may help to explain the physiological action of Heidelberg Scalp Acupuncture on brain diseases.

The reference point of HSA is called Sk0, and it is found on the skull surface from the interception of two imaginary lines going from: (1) the tip of the ear lobe and the vertex, going through the top of the skull, back to the other ear vertex and lobe; and a second line (2), going from the tip of the nose to the tip of the occiput. This point encounters correspondence with regular acupuncture point Rg20[iii] and serve as reference to find auxiliary neighboring points.
Rg20 is, if not *the* most, one of the most important points of the whole Regens conduit. Its name, acording to Porkert et al. (1999) and the HMCM[iv], *conventus omnium*, is a mention to a point, or foramen, in which *all conduits convene* - a reference to a location where all Yang conduits of the body are reunited. The point's described functions include the support of the Cardial orb, unclogging the opening of the senses, and the capacity to bring up Yang from the *lower calorium*[v]. Stimulation of this point is also described by some as a means to ameliorate forgetfulness, one of the leading symptoms of Alzheimer's Disease (Huang, Lai et al. 2007).

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i Governing Vessel acupoint - GV16

ii Secondary conduits

iii or GV20 in international nomenclature

iv Heidelberg Model of Chinese Medicine

v Reference to the anatomical location bellow the navel

3.4

TCM & NEUROLOGY

According to Chinese Medicine, Neurology, per se, as a subject of human physiology, doesn't exist in the same sense, as for instance, Gastroenterology, Urology, Gynecology or other medical specialities within Western Medicine. Most neurologic vegetative functions are mentioned within the whole system of the orbs, the agents and the ALT[i].
In view of this premise Greten (2011) quotes five theoretical considerations concerning neurologic aspects within TCM:

1. In the ambit of the HMTCM[ii], the *mind* is expressed as a semi-autonomous group of signs and symptoms related to general functions associated with the brain, hence, it is not considered even as an complete orb[iii], but a paraorb - *paraorbis cerebri* - whose manifestation occurs within the Renal orb, in the phase Water. Vegetative functions such as memory, brain processing speed, velocity of thinking and awareness, are therefore included in this specific paraorb.

2. In the system of the orbs, the Cardiac orb is the counterpart of the Renal orb. As a result, a part of these neurological functions, like the Shen[iv] emanate from the Cardiac orb. Hence, the *paraorbis cerebri* is therefore dependent of the Yin, as the Yin is depicted by the Renal orb and its counterpart, the Yang, is represented by the Shen, whose functions are dependant of the Cardiac orb.
In this reasoning, if there is a structural damage to the Yin caused by factors like age, trauma, infections, or others, the Yang will also suffer from this imbalance, resulting in a disturbance of so called higher nervous functions - the Shen.
In order to understand this relation, lets consider the example of Dysarthria - According to TCM, in Dysarthria there is an imbalance in the control of the muscles of the tong and jaw, accompanied by difficulty in mental word finding. This is both a problem of the Cardiac orb with Shen disturbances (incoherent thoughts), and also a Renal orb problem (with a structural lesion of the speech area - *paraorbis cerebri*).

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i Algor Ladens Theory or Shan-Han-Lun

ii Heidelberg Model of Traditional Chinese Medicine

iii an orb is not an organ but an organ pattern

iv The concept of Shen comprise the ability to create mental presence, emotional associativity, coherence of speech, fluent fine motrics as well as the capacity to establish of a primary order of emotions

3. Renal and Cardiac orbs are antagonistic phases, counter-balancing each other functions. Any disturbance in this equilibrium is identified as a *Cardio-Renal rapport problem*. This observation explains how a deficient Water phase (the Renal orb), may lead to neurological signs, as the Yin isn't able to balance the Yang (Yang in this case reads Shen).

4. The mathematical representation of the system of the phases is a sinus wave, with its upward movements where sympathetic functions prevail, and compensating downward movements, where parasympathetic autonomous nervous system prevails (Figure 1). If this upward movement is insufficient this might lead to lack of muscular power (the Hepatic orb) and lack of Xue[i]. This lack of Xue in turn, results in a lack of Qi, as Qi is obtained from Xue.

5. Finally, a regional lack of Xue, according to the application of the second guiding criteria of the diagnose from the HMTCM results in Algor and in this particular case, the therapeutical strategy should be addressed in line with the model of six stages - Algor Ladens Theory[ii].

In accordance to the above postulates, the general focus of a Neurological treatment should be to strengthen the Renal and Cardiac orb (first and second considerations), open the Qi pathways between them in order to accomplish counter-regulation (third consideration), and support Xue and Qi (fourth and fifth consideration) (Greten 2011, Greten 2012).

Other scholars follow a similar reasoning. Gongwang (2006), for instance, describes three possibilities concerning the origin of congenital dementia:

a. Deficiency of Liver and Kidney, case where symptoms include dizziness and tinnitus, lassitude, diminished intelligence, poor memory and impaired judgement;

b. Turbid phlegm blocking the orifices, case where the patient experiences

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i Remember that the Xue in translated as the functional vegetative capacity bounded to body fluids with functions to nurture, moisten, warmth and bring Qi to the tissues - in western medicine this concept is similar to the effects of microcirculation and the blood

ii In classical TCM, the Shan Han Lun

diminished intelligence, distention and fulness of the abdomen, heavy saliva production and heaviness feeling in the head, lassitude, lack of hunger and presents dull eyes. The basis for this assumption **b** lies on the fact that Spleen deficiency causes dysfunction[i] in the ability to *bring the clear up*. Therefore, an insufficiency of spleen will result in stagnation occurring mainly in the middle caloric region (belonging to the Tricaloric orb), and lassitude, due to the fact that the Spleen is unable to *bring the Yang up*, or, in other words, unable to bring up the energy;

c. Obstruction in collaterals conduits by stasis of blood. Again like other theories precluded, the normal function and nourishing effect of Xue is of foremost importance to avoid neurological diseases. In this particular case **c**, the symptoms encompass "dull spirit", diminished intelligence, forgetfulness, incoherent speech, strange and erratic behavior, numbness of the limbs among others. This in all results in a treatment principle compelling the restoration of consciousness by unblocking the pathways, promotion of blood circulation by draining collateral conduit system, and supporting the Kidney.

3.4.1

TCM on Dementia and Current State of the Art

Referring to the major subject ACUPUNCTURE, from 1991 to 2009, 3975 articles were published in 927 different journals. According to the Journal of Citation Reports™ the compiled output data on acupuncture research, falls into a total of 117 subcategories, from which the top subjects include **Neurosciences** with a whooping 19%, and **Clinical Neurology** with 13% (Lee, Shin et al. 2009).
This data might lead to the assumption that Brain diseases, Neurocognitive disorders including Dementia or Alzheimer would arouse more interest than they actually seem to do… In fact, at first glance the subject doesn't even seems to be very exciting to investigators - a simple search on pubMed[ii], using the words "Dementia" AND "Acupuncture" reveals no more than 156 articles. When narrowing the search criteria to "Alzheimer" AND "Acupuncture", that number diminishes to 71 results, and from these, only 55 use humans as experiment subjects.

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i The function of the spleen acording to TCM is associated with the capacity to extract nutrients from the food, turning digested food from the stomach into nutrients and Qi, promoting blood formation, assisting water metabolism and bringing the Yang "up"

ii The search was performed on 6/March/2014

Despite this modest values, on WHO[i] (2002) guidelines regarding the usage of acupuncture, in its section two (*Diseases, symptoms or conditions for which the therapeutic effect of acupuncture has been shown but for which further proof is needed*), we can read "Vascular Dementia", as well as in other sections - "Depression" -, a symptom frequently seen in these patients.

A review of Randomized Control Trials (RCT) from 17 databases until the year 2008 to evaluate the efficacy of needle acupuncture in the treatment of Alzheimer's Disease on Humans, only yielded 3 out of 40 articles that met the desired quality criteria, and all of them showed some type of shortcomings in terms of reported methods of randomization and allocation of subjects (Lee, Shin et al. 2009).
Even broadening the scope of the analysis to *Dementia*, a similar conclusion is supported by other reviewers (Peng, Wang et al. 2007). In the absence of quality randomized control trials, meta-analysis are scarce and inconclusive, suggesting the need for randomized double blinded placebo experiments.

According to Han (2007), normal aging process can be explained by the abnormal function of the Tricaloric orb[ii]. Chinese Medicine establishes that this specific orb, acts, first of all, as a pathway for the entering and exiting, ascending and descending of Qi. Secondly, that this orb is co-responsible for the production of this form of energy (Qi), essence (or Jing[iii]), blood and body fluids; and thirdly, that the normal activity of intimal orbs, (Liver, Heart, Spleen, Lung, Kidney and Pericardium), necessary to life activities, is dependent on the Qi activity on the Tricaloric orb.
This author proposes the regulation of Qi activity within the Tricaloric orb as a conceivably good strategy to delay aging and prevent senile diseases.
His proposed theory, entitled "*Principle of Tonifiing Qi and Regulating Blood, Supporting the Root and Fostering the Source*", consists of using several acupuncture points, such as CV17, CV12, CV6, TE5, ST36, and SP10. The first three points would serve the purpose of regulating the upper, middle and lower caloric, TE5 is used as a means to regulate the whole Tricaloric orb, ST36 to

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i World Health Organization

ii Triple Energiser in international nomenclature

iii Jing is defined by the HMTCM as the structive potential and its effects which are analogous to the effects of the nuclei of the cell, including donating the functional repertoire of the cell via DNA and reproductive functions, according to the Heidelberg Model of vegetative regulation

support the constitutional diagnosis and SP10 to supplement and harmonize the blood .

The understanding of the underlying mechanism by which acupuncture acts on neurological diseases is paramount to the development of an assertive therapeutical approach. Several researchers draw attention to the its effects and mechanism on mild cognitive impairment and Alzheimer's disease (Guo, Shi et al. 2002); (Zhou, Han et al. 2008); (Zhou and Jin 2008); (Feng, Bai et al. 2012); (Wang, Nie et al. 2012); (Zeng, Salvage et al. 2012); (Zhu, Guo et al. 2012); (Sutalangka, Wattanathorn et al. 2013); (Zhang, Yu et al. 2013) ;(Liu and Fu 2014) (Sun, Luo et al. 2014).

Zhou & Jin (2008) analyzed various regions of the brain of Mild and Moderate AD diagnosed patients before and after acupuncture. In their study, twenty-six patients diagnosed with AD and a mean age of 71.6 years, were submitted to electroacupuncture interval stimulation on HT7, ST36, ST40 and KI3, while their brain was being scanned via fMRI[i].
Results showed both right and left brain hemisphere activations within areas related to cognition, contributing to support good evidences of the usage of acupuncture on AD patients and the possible mechanism by which these improvements occur.

Similar results where obtained by Zeng et al. (2012) Also recurring to functional brain images, the researchers were able to expose increases and decreases of activity prior to acupuncture, on areas are closely related to memory and cognition that usually present abnormal functional connectivity on patients with Mild Cognitive Impairment and AD, namely on the temporal and prefrontal lobe.

The principle of needle retaining had already been mentioned in the oldest medical book of Chinese Medicine - *Yellow Emperor's Inner Cannon*. The benefits of this practice, called Acupoint Thread Embedding (ATE), are identified as both the potential to attain a more powerful effect as to maintain it for longer periods of time (Sun 2012).
The technique was tested by Zhou et al. (2008) on AD patients using acupoints

i functional Magnetic Resonance Imaging

HT7, ST36, ST40 and KI3. ATE was performed once a moth for a total of 6 months on half the patients, whereas the other half received Sham acupuncture.
By comparing scores of MMSE and ADAS-cog before and after treatment, correlation between fMRI and cognitive ability was assessed. The results showed a statistically significant improvement on MMSE score, when compared to the sham group and a statistically significant decrease on ADAS-cog, both evidences of cognitive improvement, further confirmed by fMRI observation of activations in frontal, temporal lobe, cerebellum and marginal system, supporting the beneficial effect of ATE on patients suffering from AD.

In a recent study, Wang et al. (2012) found similar results using different acupoints than Zhou (Zhou, Han et al. 2008, Zhou and Jin 2008). These investigators compared brain fMRI images of Mild Cognitive Impairment (MCI) and AD diagnosed patients versus healthy controls, while puncturing KI3 and LI4.
By analyzing data retrieved before, during and after acupuncture, Wang et al. found significant differences between the groups, with AD and MCI patients showing activations in regions consistent with brain function impairment, namely on temporal and frontal lobes, supporting the fact that the usage of these points may activate cognitive related brain areas.

These results also con-substantiate those obtained on animal models, where specific acupoint stimulation is believed to cause trophic factor release[i], enhance cholinergic transmission, diminish apoptosis and oxidative damage and reduce A-beta proteins in brain areas such as the hippocampus of these AD models (Zeng, Salvage et al. 2012).

When reviewing the progress of experimental research on the therapy of AD using acupuncture, Liu & Fu (2014) summarized the mechanisms by which AD is treated in animal models.
Their work points to several strategies, among which the reduction of beta-amyloid protein, attenuation of phosphorylation of tau protein, regulation of neurotransmitter dysmetabolism and oxidative stress, reduction of neuron apoptosis, inhibition of glial cells differentiation, adjustment of G protein signaling transduction, and normalization of mitochondrial dysfunction.

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i Trophic factors are responsible for the development of certain neurons within neural networks

A similar outcome had already been revisited by Zhu et al. (2012), on a review from which the authors preclude the need for syndrome differentiation when approaching acupuncture therapeutic strategy in order to clarify its mechanism on AD.

Zhang et al. (2013) resorted to Senile Accelerated Mice in order to analyze the effect of *"Sanjiao Acupuncture Therapy"* on hippocampal neuron loss and astrocytosis of glial cells. They concluded that the therapeutic strategy, consisting on the stimulation of CV17, CV12, CV6, ST36 and SP10, contributed decisively to reduce, or at least delay neuron loss, suppress astrocytosis and regulate the relation between neuron and astrocyte.
The authors noted increases of cerebral blood perfusion, relating it to improvements in terms in spacial learning and memory of the test subjects, arguing that the augmented blood supply would therefore reduce the formation of reactive oxygen species, resulting in those measured cognitive improvements.

Following this previous work, Zhang, et al. (2014) demonstrated the improvement of cognitive abilities among rats with Multi-Infact Dementia, shedding some light on a possible acupuncture neuroprotective effect over oxidative stress and chronic hypoperfusion of the brain (major risk factors in the development of dementia).

After injecting beta Amyloid protein on the hippocampus of Wistar rats in order to develop suited AD models, Sun et al. (2014) tested the effects of acupuncture and moxibustion, on ultrastructure and Silent Information Regulator 1[i], on hippocampal neuron mitochondria.
By using GV20 and BL23 acupoints and analyzing the results, the researchers found that within the acupuncture group, both the ultrastructure in hippocampal neuron mitochondria was improved, as also SIR1 increased, promoting the recovery of injured mitochondria.
In a complementary work, the same authors found that the proposed therapy was able to reduce over-expression of Abeta-binding alcohol dehydrogenase[ii], therefore improving hippocampal neuron mitochondria energy metabolism.
Once again, supporting the kidney, in this particular case, via acupoint BL23,

i Silent Information Regulator 1 is a histone deacetylase which has been reported as having neuroprotective effects on neurological diseases

ii An enzyme found in neuronal mitochondria, which increases molecular mitochondrial free radicals

seems to yield effective results in AD.

Sutalangka et al. (2013) focused their research on the beneficial effect of laser acupuncture at acupoint HT7 on learning and memory function.
Resorting to animal models, the authors started by inducing memory impairment via injection of a cholinotoxin in Wistar rats. Both Spacial Memory, levels of acetylcholinesterase (AChE), Superoxide Dismutase (SOD)[i], Catalase (CAT)[ii], malondialdehyde (MDA)[iii], glutathione peroxidase (GSH-Px)[iv] were assessed at several time frames, to conclude that on the group receiving acupuncture, SOD and CAT significantly increased in the hippocampus but not MAD[v], suggesting that oxidative stress balance may not be so important in this cognitive enhancing effect. Despite this fact, AChE[vi] activity within the hippocampus was suppressed, thus increasing the concentration of ACh[vii]. The authors suggest that laser acupuncture at Ht7 leads to improvement in cholinergic function which in turn results in reduction of cognitive impairment within these AD animal models.

Fang et al. (Fang, Zhu et al. 2013) suggested the improvement of AD by electroacupuncture, via reduction of inflammatory reactions within the hippocampus and frontal lobe brain tissues. By submitting AD induced rats to electroacupuncture (EA) on acupoints GV20, KI3 and ST36 and comparing IL-1beta mRNA and P 38 MAPK[viii] protein expression levels in the hippocampus and frontal lobe amongst EA and sham groups, the investigators were able to demonstrate significative reduction of the over-expression of both substances in the first group, leading to the confirmation of the hypothesis that AD improvement occurs by reduction of inflammatory processes in the brain.

Using functional imaging techniques (PET [ix] and SPEC[x]), Huang, et al. (2007) evaluated the effects of blood perfusion in several areas of the brain, and by

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i SOD is an enzime found in living organisms, responsible for the removal of free radicals, therefore preventing cell damage

ii CAT is also an enzime found in living organisms responsible for the removal of the toxic hydrogen peroxide

iii Biological marker for oxidative stress

iv GSH-Px is an enzyme with oxidative damage protective effects

v Mitochondria-associated Degradation

vi Acetylcholinesterase

vii Acetylcholine

viii P38 is a Mitogen-Activated Protein kinase involved in stress reactions like cell differentiation, cell apoptosis and autophagic reactions, whereas IL-1beta is a mediator of the inflammatory cascade, also involved in cell differentiation and apoptosis

ix PET- Positron Computerized Tomography

x SPEC - Single Photon Emission Computerized Tomography

semi-quantitatively analysis, the changes of blood glucose metabolism, resulting from needling a specific combination of acupoints on Vascular Dementia patients. The points chosen by the team included LI15, LI11, TE5, LI4, SP10, ST36, SP6, HT3, plus other three points, pricked individually and in combination - GV20, GV26, HT7.

Interpolating the results obtained from MMSE[i], ADL[ii] and FAQ[iii] and the outcome of the imaging techniques and glucose metabolism, they aimed to understand the differences and specificity of using those three additional points (GV20, GV26, and HT7).

Although these authors deliberately excluded patients with Alzheimer's Disease, the results may yet be important to the present study, since they might shed some light on the therapeutic strategy to pursue as well as the acupuncture mechanism underlying acupuncture usage in Dementia.

The investigators proved that needling those three additional acupoints, showed several benefits in patients with Vascular Dementia, with diverse functional directions: the tests performed using GV20 showed more pronounced effect on temporal lobe, diencephalon and prefrontal cortical system, prone to improve memory and executive capacity; with GV26 the effect was more towards the prefrontal cortical system, enhancing executive capacity, and when combining conventional therapy with HT7, the effect was similar to the one obtained with GV20, although weaker in power.

The study concludes that combing the three namely acupoints, could positively influence multiple nervous system functions related with cognition and intelligence on Vascular Dementia patients.

Resorting to fMRI to identify abnormal connectivity areas of the brain, among patients diagnosed with MCI[iv] and Healthy Controls (HC), Feng et al. (2012) tested the effects of Deep Acupuncture (DA) versus Superficial Acupuncture (SA) on KI3. Following previous investigations, the authors found abnormal connectivity in regions related to memory within the MCI group in the resting state, namely in the temporal area (hippocampus, thalamus, fusiform gyrus) and prefrontal cortex.

When comparing DA and SA, results suggest that acupuncture is able to modulate

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i Mini Mental State Examination

ii Activities of Daily Living

iii Family Attitude Questionnaire

iv Mild Cognitive Impaired

abnormal region's connectivity within MCI patients, with this effect being stronger when using DA needling.

Lombardo et al. (2001) studied the effects of acupuncture on the treatment of depression and anxiety in patients with Alzheimer Disease (AD) and Vascular Dementia (VD).
Eleven patients, with a mean combined age of 76 years and mean MMSE scores of 22.4, ten diagnosed with AD and one with VD, were evaluated after a minimum of 22 acupuncture treatments chosen accordingly to six diagnostic categories of TCM. Used points included GV20, KI3, ST36, Sishecong[i], Yintang[ii], SP6, HT7, GB9 and GV23 and measures of assessment included the Cornell Scale for Depression in Dementia (CSDD), the Speilberger State Anxiety Inventory, and the Mini-Mental Status Examination.
The results yielded significative improvements in all of the Anxiety scales used, but regarding Depression, only on CSDD the differences were statistically significant. Despite the fact that cognitive function had not been tested, some caregivers reported improvements in the subjects thinking abilities, maybe indicating a close relationship between cognitive ability, anxiety and depression.

In another study, designed to evaluate the effects of acupuncture on AD, eight patients categorized according to TCM diagnostic criteria for Alzheimer's Disease and MMSE scores, achieved higher rates on the respective neurocognitive scale, after being submitted to acupuncture on Sishecong, HT7 and KI3 bilaterally, on a seven day treatment cycle, after a total of 30 days, indicating a significative improvement of cognitive function (Kao, Wang et al. 2000).

Guo et al. (2002), tested the effects of Transcutaneous Electrical Nerve Stimulation (TENS) on cognitive function and short-term memory in patients with AD.
In previous studies using this technique, it had been suggested that TENS could possibly activate the hippocampus and hypothalamus.
Guo and its colleagues set the electrodes on BL1, an acupoint believed to enhance the effect of ACh. Fourteen elderlies diagnosed with mild and severe AD, with mean age 77.2 years were subjected to TENS every other day for a total of four

i Name atributed to a combination of 4 points located 1 cun anterior, posterior and lateral of GV20
ii Extra point located in the course of the Gorverning Vessel conduit, between the eyebrows

weeks.
The cognitive function was measured via the revised Hasegawa's Dementia Scale (HDS-R), and short term memory via a seven picture test (SMT-7) designed by the research team. The neurocognitive test (HDS-R) was performed before and after the treatments, and also 6 months prior to its end in order to assess long-term effects. Results depicted significative improvements on HDS-R and SMT-7, specially on mild AD diagnosed patients after the fourth week treatment, but they were not held after the six month period.

About the effectiveness of scalp acupuncture

In the past, typical uses of Scalp acupuncture were closely related to cerebral and neurological diseases, due to the specific location of acupoints in manifold areas of the brain (Dharmananda and Vickers 2000). This restrictive focus of the usage of SA[i] to nervous system disorders is still prevailing among several practitioners, although in later years this spectrum has been broadly increased to incorporate several other diseases besides those related to the brain.

Randomized Control Trials of SA for Acute Hypertensive Intracerebral Hemorrhage were reviewed by Zheng (2011). Although no scientific evidence was found in regard to the outcome of death or dependency at the end of long-term follow-up (3 months), in patients who survived, the authors found improvements on the recovery of the neurological deterioration presented as a consequence of the disease.

Lee et al. (2013) compared the efficacy of known SA models versus conventional therapies (pharmacological, physical and deep brain stimulation) on Parkinson's Disease (PD). Yielding a total of 185 Parkinson's Disease patients, the researchers concluded that albeit not entirely convincingly, (mainly due to methodology issues), effects of SA on PD seemed a promising valid therapeutical approach.

In a pilot study, Allam and his peers (2008) compared the efficacy of combined Scalp Acupunture and Language Therapy (LT) vs Language Therapy alone in 20 Autistic children, to show superior significant improvements in cognitive function, attention as well as in expressive language on the combination test

i Scalp Acupuncture

group. Both Yamamoto New Scalp Acupuncture (two needles - cerebrum and aphasia acupoints), temple zone acupuncture (two needles) and three classical acupuncture points were used - GV20, GV26 and GV17. The needles were retained in place for 20 minutes, on a twice a week basis regimen for two months, followed by another two months rest with a total of nine months experimental duration.

Patients suffering from Dementia also seem to benefit from SA. Investigators showed marked improvements in terms of the cognitive deficit measured by the Mini Mental State Examination test, on mild to moderate Dementia patients subjected to electric scalp acupuncture stimulation when compared to body acupuncture (Huang, An et al. 2012).

The effects of acupuncture in AD are not uncontroversial, with some authors arguing that poor results and confounding investigations are the result of a generalized lack of scientific quality.

Randomized Control Trials within this particular subject are scarce, and just a few of those have cut clear methodologies or even sufficient patients to guaranty scientific validity (Ernst 2006); (Lee, Shin et al. 2009).

Despite that fact, some results and clinical experience are encouraging enough to lead new investigations in this area.

Although there is no cure for Alzheimer's Disease, research shows that both Western Medicine pharmacology, as well as Traditional Chinese Medicine, may improve the outcomes of the disease by reducing the magnitude of the impairments that come with the rather complicated pathology, thus delaying the patients loss in terms of quality of life.

4

STUDY ARGUMENTS, OBJECTIVES AND HYPOTHESIS

Arguments

Pharmacological treatment in Alzheimer's Disease is still somewhat unsatisfactory. Science hasn't yet found a way to revert the symptoms, and particularly in more advanced stages of the disease, the overall therapeutical benefits are not sufficient for these patients to live an autonomous life and perform their daily activities on an individual basis.

As the literature review shows, acupuncture has already exhibited some positive effects on AD animal models and patients, however, human clinical trials are yet scarce and those that are published, usually rely on small sized samples.

Studies on the subject of acupuncture for AD resorting to imaging techniques like fMRI, have definitely contributed to current state of the art by providing possible physiological explanations regarding the mechanisms of acupuncture in patients suffering from the disease.

To the best of our knowledge, no investigation on Heidelberg Scalp Acupuncture for Alzheimer's Disease has been published. Given the neurobiological plausibility of SA effects and its positive clinical outcomes, it is also possible that the technique exhibits beneficial effects on Alzheimer's Disease.

Objectives

a.To evaluate the effect of Heidelberg Scalp Acupuncture (HSA) on the cognitive function of Mild to Moderate Alzheimer's Disease patients in a preliminary trial.
b.To assess the feasibility and effectiveness of the research protocol for a future clinical trial.

Expected Results

We expect that HSA positively contributes to improve cognitive function in patients with Alzheimer's Disease, which being the case, might lay ground for a future multi-centric, randomized clinical trial, with a double-blinded controlled design.
From previous research, it is also expected that these effects will be more pronounced among patients diagnosed with Mild to Moderate stages of the disease.

If HSA shows good results, it may then be used by physicians as an additional therapeutic tool for the conventional treatment of Alzheimer's Disease.

Research question

Does HSA improve cognitive function in Mild to Moderate AD medicated patients?

Study hypothesis

Are there any significative differences in cognitive function of Mild to Moderate AD diagnosed patients, when they are subjected to HSA in addition to their pharmacological therapy?

a-MMSE

H0a	There is no statistical difference in the score of MMSE before and after HSA μDifferences=0
H1a	There a statistical difference in the score of MMSE before and after HSA μDifferences≠0

b-ADAS-cog

H0b	There is no statistical difference in the score of ADAS-cog before and after HSA μDifferences=0
H0b	There is a statistical difference in the score of ADAS-cog before and after HSA μDifferences≠0

5

PRELIMINARY STUDY

5.1

RESEARCH TEAM

Main investigator

Carlos Reis, Pharmacist
Degree in Pharmaceutical Sciences
Specialist in Community Pharmacy
Master student in Traditional Chinese Medicine – ICBAS-UP[i].

Co-investigators

Pedro Carneiro, MD
Specialist in Neurology - Hospital Santos Silva, Centro Hospitalar Vila Nova de Gaia/Espinho; Neurology Outpatient Clinic – Hospital da Santa Casa de Misericórdia, Marco de Canaveses.

Nuno Correia, MD
Specialist in Internal Medicine – Emergency Service, Hospital São João, Centro Hospitalar São João, Porto
MSc in Traditional Chinese Medicine

Research supervision

Professor Henry Johannes Greten, PhD, MD
Director of the TCM Master Program – ICBAS-UP
Head of the Heidelberg School of Traditional Chinese Medicine;
President of the German Society of Traditional Chinese Medicine (DGTCM[ii]), Heidelberg, Germany.

Co-Supervisor 1- Dr. Pedro Carneiro.
Co-Supervisor 2 - Dr. Nuno Correia.

i Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto
ii on the original - *Deutsche Gesellschaft für TCM*

5.2

PROCEDURE

5.2.1

Ethical Considerations, protection of Human subjects and assessment of safety

Ethical Considerations

All patients voluntarily decided to be a part of the present study. Participants were not given or promised any warranties regarding their heath after or during the study.

The study was conducted in accordance to the 1964 Helsinki Declaration and international standards of Good Clinical Practice requirements and it was granted approval from the Ethical Committee (EC) of Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto (Annex 1) and positive feedback from Hospital da Santa Casa da Misericórdia de Marco de Canaveses (Annex 2).

All participating subjects were provided a consent form, describing the study with precise information, in order to exert an informed decision about their participation in the investigation (Annex 3).
In any case where the patient's cognitive state was dubious regarding their judgement capacity, the consent and further explanations were presented to the families or legal surrogates.

Subjects and/or families were briefed about the goals, methods, objectives, and potential risks or discomforts, as well as that it was their right to decide to withdraw or discontinue the experiment at any moment during his/her participation. They were also notified that no prejudice would result in case of refusal to participate or withdrawal from the study.

No interference with clinical decisions occurred. Dr. Pedro Carneiro, as the patient's clinician, was asked, if feasible, to avoid any changes in the patient's current medication during the study time frame.

The incidence of adverse effects of acupuncture in multiple studies is residual. Regarding this issue, subjects were asked about adverse experiences at each visit, defined as any unfavorable and unintended sign, symptom or disease temporally associated, (or not), with the use of the acupuncture treatments.

In any case, the trial would stop if the investigators believed that there was an unacceptable risk of serious adverse events.

Confidentiality

All data collected in the scope of the present study is confidential, and identification of participants was preserved at all moments. Data will only be maintained during the necessary time to produce the present paper.

Participants Exemption

No pre established agreement existed that obliges participants to take part in the study. Both patients and other participants were free, at any given moment, to abandon the investigation if this was their desire.

Financing and Conditions

This study is independent and as such, not financed by any institution. Participants were voluntarily a part of it, without any promise of financial or other form of compensation.
The resulting costs of investigation were fully and solely supported by the investigator.

Conflicts of Interest

None of the individuals that were part of the present study was involved in any conflicting activity.

Authorizations

The present study started after granted approval from ICBAS-UP Ethical Committee (Annex 1), with positive feedback from Prof. Henry J. Greten, in the quality of research supervisor (Annex 4), Dr. Pedro Carneiro as co-investigator and Prof. Amélia Ferreira, institutional representative of *Hospital da Santa Casa*

de Marco de Canaveses (Annex 2).

5.2.2

Intervention report

In order to retrieve preliminary data to serve the purpose of defining a future assertive methodological protocol, an initial batch of patients suffering from AD were screened.

Dr. Pedro Carneiro, as an independent Neurologist within HSCMMC, was asked to identify patients he thought might be interested in participating in the present study, after the assessment of the proposed eligibility criteria (Table 9).

Inclusion criteria	**Exclusion criteria**
1-Male or female patients, 40 to 90 y.o., with confirmed diagnosis of Alzheimer's Disease, Possible or Probable according to the diagnostic criteria of the DSM-V and NINCDS-ADRA (American Psychiatric Association - DSM-5 Task Force 2013) (McKhann, Drachman et al. 1984) *2-Neurocognitive MMSE test score between 10 and 24 (moderate AD: 10-18; mild AD: 19-24)* *3-Patients under stable pharmacological conventional treatment (> 3 weeks)* *4-Informed consent signed by patient or legal substitute.*	*1-Diagnosis of mixed Dementia and Alzheimer's Disease, or other Dementia type besides Alzheimer* *2-Previous brain lesions that may influence cognitive function.* *3-Epilepsy or other neurological chronic disease.* *4-Any acute disease* *5-Unstable at-risk patient* *6-Hematological disease*

Table 9 - Eligibility criteria[i]

After granted authorization by the ICBAS-UP Ethical Committee (Annex 1), and HSCMMC (Annex 2), 14 patients were selected, from which data was collected regarding their *age*, *gender*, *educational level* as well as *current stable medication for AD*.

Patients were contacted by the main investigator, in order to evaluate their

i Given the reduced number of participants, as will be seen later on, the researchers agreed on accepting one patient with an initial MMSE score of 25 points

availability and willingness to incorporate the study.
All of these initial contacts took place by phone, and considering these patient's health condition and age, whenever possible, conversation took place between the investigator and the patient's caregiver.

The caregiver was, in most cases, a close relative to the patient, to whom the experiment was thoroughly explained. The investigator started by introducing himself as a researcher working in partnership with the patients' neurologist[i], and a referral was made to Hospital da Santa Casa da Misericórdia de Marco de Canaveses (HSCMMC).
In some of the cases, the caregivers knew or remembered the patient's doctor, and that being the case, they were immediately asked if they had the habit of accompanying the patient to his neurology appointments at the hospital - this served the purpose of diminishing initial reservations and easing the introduction of the experiment, given that in most cases, caregivers had already witnessed any form of neurocognitive test administration, which in turn allowed the investigator to state that part of the experiment was a common task, already familiar to the patient.

After surpassing this initial barrier, with the caregivers' confidence level in the investigator a bit higher than before, we addressed the purpose of the investigation, and the subject of scalp acupuncture was introduced. The technique was explained, as well as the research goals and expected results.

If the caregiver agreed to address the patient regarding the investigation, they were told that every question or doubt would be answered in an up close personal interview, without any further obligation of the patient to take part in the present study.
They were also assured that no cost was due in terms of the experiment[ii], and that there was no need to dislocate the patient - with their permission, the investigator would go to the patients's house, and perform the experiment right there, in order to minimize disturbance in their daily routines.
After receiving this information, several caregivers asked to be re-contacted after

i Dr. Pedro Carneiro

ii More than once we were asked about the cost of the intervention and the place where the caregiver should bring the patient to receive the "treatment"...

a day or two, in order to give them time to address the patient regarding the study.

Over the course of the second contact, impressions, arguments and refusal reasons were collected for further scrutiny (see Table 10). Within those that agreed to incorporate the study, or others, that despite not entirely convinced, allowed us to speak with the patient explaining them the experiment ourselves, we scheduled a time and day to perform a personal interview.

Patient number	Booking Date	Id	Gender	Age	Scholarship	Medication (stable)	Contact	Refusal base
3	16/9	A.S.	M	76	Undergraduate 4th Grade	Rivastigmine™ 9,5mg transdermic patch	Wife	
-	-	J.L.	F	78	-	Rivastigmine™ 9,5mg p.o. Onlazapine™ 5mg p.o. Quetiapine™ 100mg p.o.	Daughter	"my mother didn't allow"
1	16/9	G.S.	F	80	Higher Education	Donepezil™ 10mg Levitiracetam™ 250mg	Daughter	
-	18/9	T.N.	F	74	-	Rivastigmine™ 9,5mg transdermic patch	Daughter	The daughter spoke to the wife's husband and he refused to allow the study.
-	16/9	J.P.	M	81	-	Donepezil™ 10mg p.o.	Son	The son argued that life was too complicate it the present time (sic), and we would increase family discomfort by submitting his dad to the study.
-	16/9	M. P.	F	83	-	Donepezil™ 10mg p.o.	The patient	Doesn't authorize - It was rather difficult to introduce the study via the phone and the patient didn't authorise a presencial interview
5	17/9	M.R.T.	F	72	Undergraduate 3rd Grade	Donepezil™ 10mg p.o.	Daughter	
6	18/9	M.A.M.	F	80	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	Daughter	
-	16/9	M.S.	F	81	-	Memantine™ 10mg	Daughter	The patient has hematological disease
2	17/9	M.M.	M	84	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	Wife	
-	17/9	J.S.	F	81	-	Rivastigmine™ 9,5mg transdermic patch	-	-
-	17/9	M.S.	F	86		Donepezil™ 5mg p.o.	Sister-in-law	The patient is currently in the hospital due to acute disease
4	17/9	M.A.C.M.	F	79	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	Daughter	
-	16/9	M.R.	F	81		?	Daughter	The patient refused based on her fear of needles

Table 10 - Patients recruitment and data before intervention

In these interviews that took place, patients and caregivers were present along with the investigator.

Whenever the subject's mobility was not an issue, we kindly asked for a quiet room to explain the experiment, which regardless of the request, resulted in some conversations occurring in the patients bedroom, with the patient lying in

bed.

The procedure was carefully explained once again, but this time the speech was deliberately directed to the patient.
If both caregiver and patient agreed to the experiment, informed consents were introduced and read out loud, before signed.

Protocol Administration

Points to prick during the preliminary study were suggested by Prof. Henry J. Greten, based on the Heidelberg Clinic of Chinese Medicine clinical expertise group treating Alzheimer's Disease patients.
Seven gold scalp acupuncture needles were placed on the patient's skull, on the so called *seven chakras* area, starting by the reference point located at GV20[i]. From this point forward, six other needles were placed, on anterior direction, distant by 1 (one) Scalp Acupuncture *cun*[ii] from the previous. The needles were then retained for a period of three days, after which they were removed and neurocognitive tests repeated.

-following the previous paragraph-

If the patient had available time at that first interview, the first part of the protocol was immediately applied - both MMSE and ADAS-cog were performed, and at the end, scalp acupuncture needles were put in place. If not, a future session was scheduled in order to initiate the procedure.

Whenever necessary, a picture of the patient scalp was taken and immediately shown to the patient, to reduce any awkward feeling (Picture 1).

Subjects were also advised that no change in their regular daily habits was needed and that it might be normal to loose some needles during the three day trial.
An A4 sized sheet of paper with the investigator phone number was left near the phone, in case the patient or the caregiver felt the need to report anything out of

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i GV20 is obtained from the intersection of two imaginary lines going from: the first - the tip of the ear lobe and the vertex, through the top of the skull, back to the other ear vertex and lobe; and the second - from the tip of the nose to the tip of the occiput.

ii The *cun* is a relative measuring unit used in Traditional Chinese Medicine to accurately locate acupoints.

the ordinary, (or ordinary), until the next interview, three days later.

Picture 1 - Photos of placed needles on the patients' skull after interview on day one

During the three days retaining period, any contacts, comments and impressions were collected for further analysis. On the third day, neurocognitive tests were repeated after needle removal and their scores were collected. Following the tests, a structured interview was initiated with the patient and the caregiver to retrieve any further impressions felt during test period.

Every now and then, we were asked by the caregiver or the patient himself, if their condition[i] was "better or worse". - regarding this issue, no assumptions were made or told and any remaining questions regarding that particular subject were redirected to the patient's physician on a following appointment.

Before leaving, we gently recognized the patients's and caregivers enrollment on the project, acknowledging their effort and emphasizing the major importance of their contribution. No contact was made ever since with any of the participants.

i The questions posed relate to the AD condition, or the score of the test. "What do you think" or "Is he better?" or "Was there any improvement" [sic]

5.3

RESULTS

Six Alzheimer's Disease patients, 4 female and 2 male, with mean age 78.5 years old, agreed to participate in the current preliminary study.

Out of the 14 inquired patients, more than half (8) refused to participate in the study. Objectively shared refusal reasons included patient's *fear from needles*, *lack of time to perform the intervention*, *inconvenient momentum*[i], *hematological disease* (eligibility criteria) and *sudden acute disease* (eligibility criteria).

From an subjective stand point - interpreted by the researcher although not objectively declared by the patients or caregivers -, at least two other reasons may be pin pointed: *lack of confidence in the researcher or the procedure*, due to inability of the researcher to clearly explain it over the phone[ii] and *lack of previous knowledge of the experiment by the patients' current neurologist.*

Patients' impressions and remarks on the study and any particular feelings that might have occurred during the test phase were registered, as well as results from Neurocognitive tests scores, performed previously and after the intervention (Table 11).

Descriptive statistics[iii] are presented on Tables 12 to 16, considering a confidence interval of 95% (alpha = 0.05).

Neurocognitive tests results

MMSE scores before the intervention ranged from **10** to **25** points with a mean value of **18.17 points**, and after the intervention, between **19** to **26**, with an average value of **22.00 points** (Table 12).

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i One caregiver mentioned understanding the importance of the study, but at the present time he was too absorbed into taking care of his father, who was one of the Alzheimer's Disease patient's, her mother, who had recently lost her mobility while fighting to maintain the job he was about to loose, because of the time he spent everyday taking care of both. We think its important to detail this honest answer, which in fact, supports the thesis that caregivers face a huge burden dealing with the non immediate costs of the disease

ii All of the refusals occurred via the phone. In all of the cases when the investigator was given the chance to explain the procedure on a personal interview, the individuals accepted to take part of the study

iii Statistical analysis was performed resorting to statistical software IBM SPSSStatistics™ version 21

MMSE average score (points):

18.17 **before** **=> 22.00** **after**

ADAS-cog values before the intervention ranged between **18** to **43**, with a mean value of **30 points**, and after the intervention between **14** to **37** with an average value of **25.33** points (Table 13).

ADAS-cog average score (points)

30.00 **before** **=> 25.33** **after**

Normality adherence tests

Due to the small sample size (N=6), normality adherence tests were performed.

Normal distribution of MMSE and ADAS-cog is supported by the significance level of the Shapiro-Wilk test, which in both cases is superior to 0.05 (Tables 14 and 15):

Shapiro-Wilk Sig. (MMSE_before) = 0.499 > 0.05 ***and*** *Shapiro-Wilk Sig. (MMSE_after) = 0.213 > 0.05*

Shapiro-Wilk Sig. (ADAS_before) = 0.248 > 0.05 ***and*** *Shapiro-Wilk Sig. (ADAS_after) = 0.729 > 0.05*

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Estatística	df	Sig.	Estatística	df	Sig.
MMSE_before	.222	6	.200*	.919	6	.499
MMSE_after	.241	6	.200*	.867	6	.213

*. Este é um limite inferior da significância verdadeira.

a. Lilliefors Significance Correction

Table 14 - MMSE normality test

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Estatística	df	Sig.	Estatística	df	Sig.
ADAS_before	.206	6	.200*	.875	6	.248
ADAS_after	.156	6	.200*	.949	6	.729

*. Este é um limite inferior da significância verdadeira.

a. Lilliefors Significance Correction

Table 15 - ADAS-cog normality test

The normality condition verified above, endorse's the usage of Students-T test to compare mean scores obtained from MMSE and ADAS-cog scores.

						Before Protocol		After Protocol		MMSE		ADAS		
Patient number	Id	Gender	Age	Scholarship	Medication (stable)	MMSE	ADAS	MMSE	ADAS	Difference	%	Difference	%	Observation
3	A.S.	M	76	Undergraduate 4th Grade	Rivastigmine™ 9,5mg transdermic patch	20	35	19	37	-1	**-3,33**	2,00	**2,86**	Removed the needles after the first day. He was deep asleep when we arrive at removal day, previously to the interview
1	G.S.	F	80	Higher Education	Donepezil™ 10mg Levitiracetam™ 250mg	12	43	20	29	8	**26,67**	-14,00	**-20,00**	All the needles were in place after the three day period.
5	M.R.T.	F	72	Undergraduate 3rd Grade	Donepezil™ 10mg p.o.	23	24	23	22	0	**0,00**	-2,00	**-2,86**	Six needles remaining on removal day. No symptomatology was felt during test period
6	M.A.M.	F	80	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	25	18	26	17	1	**3,33**	-1,00	**-1,43**	On the day before the first test period she had perform neurocognitive stimulation in a group session with the nursing home psychologist Six needles remaining on removal day. She felt stomach cramps, further treated with laxative and camomile tea.
2	M.M.	M	84	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	10	41	19	33	9	**30,00**	-8,00	**-11,43**	Due to discomfort felt, the patient removed the needles after day two.
4	M.A.C.M.	F	79	Undergraduate 4th Grade	Rivastigmine™ 4,6 transdermic patch	19	19	25	14	6	**20,00**	-5,00	**-7,14**	Two needles remaining after day three
			78,5							3,83	**12,78**	-4,67	**-6,67**	

Table 11 - Preliminary data

Descritivos

			Estatística	Modelo padrão
MMSE_before	Média		18.17	2.442
	Intervalo de confiança de 95% para média	Limite inferior	11.89	
		Limite superior	24.44	
	5% da média aparada		18.24	
	Mediana		19.50	
	Variância		35.767	
	Desvio padrão		5.981	
	Mínimo		10	
	Máximo		25	
	Range		15	
	Amplitude interquartil		12	
	Assimetria		-.477	.845
	Kurtosis		-1.527	1.741
MMSE_after	Média		22.00	1.265
	Intervalo de confiança de 95% para média	Limite inferior	18.75	
		Limite superior	25.25	
	5% da média aparada		21.94	
	Mediana		21.50	
	Variância		9.600	
	Desvio padrão		3.098	
	Mínimo		19	
	Máximo		26	
	Range		7	
	Amplitude interquartil		6	
	Assimetria		.303	.845
	Kurtosis		-2.331	1.741

Table 12 - MMSE descriptive statistics

Descritivos

			Estatística	Modelo padrão
ADAS_before	Média		30.00	4.531
	Intervalo de confiança de 95% para média	Limite inferior	18.35	
		Limite superior	41.65	
	5% da média aparada		29.94	
	Mediana		29.50	
	Variância		123.200	
	Desvio padrão		11.100	
	Mínimo		18	
	Máximo		43	
	Range		25	
	Amplitude interquartil		23	
	Assimetria		.083	.845
	Kurtosis		-2.537	1.741
ADAS_after	Média		25.33	3.730
	Intervalo de confiança de 95% para média	Limite inferior	15.75	
		Limite superior	34.92	
	5% da média aparada		25.31	
	Mediana		25.50	
	Variância		83.467	
	Desvio padrão		9.136	
	Mínimo		14	
	Máximo		37	
	Range		23	
	Amplitude interquartil		18	
	Assimetria		.006	.845
	Kurtosis		-1.869	1.741

Table 13 - ADAS-cog descriptive statistics

Mini Mental Status Examination

H0a	There is no statistical difference in the score of MMSE before and after HSA $\mu_{Differences}=0$ or $\mu_{MMSE\_before}-\mu_{MMSE\_after}=0$
H1a	There is a statistical difference in the score of MMSE before and after HSA $\mu_{Differences}\neq0$ or $\mu_{MMSE\_before}-\mu_{MMSE\_after}\neq0$

Estatísticas de amostras emparelhadas

		Média	N	Desvio padrão	Erro padrão da média
Par 1	MMSE_before	18.17	6	5.981	2.442
	MMSE_after	22.00	6	3.098	1.265

Correlações de amostras emparelhadas

		N	Correlação	Sig.
Par 1	MMSE_before & MMSE_after	6	.712	.112

Teste de amostras emparelhadas

		Diferenças emparelhadas					t	df	Sig. (2 extremidade s)
		Média	Desvio padrão	Erro padrão da média	95% Intervalo de confiança da diferença				
					Inferior	Superior			
Par 1	MMSE_before - MMSE_after	-3.833	4.355	1.778	-8.404	.737	-2.156	5	.084

Table 16 - MMSE T-test statistics

The correlation analysis depicts a value of 0.712, but a significance level of 0.112, higher than the alpha value (0.05), which doesn't allow the rejection of the null hypothesis, meaning in this case, that the correlation is not significative.

Computing the results from the T-test for paired samples, we obtained a mean difference of -3.83 points (22.00-18.17), but again with a significance level (p-value) higher than alpha - 0.084>0.05 - which once more, doesn't allow the exclusion of the null hypothesis (H0a).
Therefore, the mean difference obtained (-3.833) is not statistically significative considering a 95% confidence interval.

Alzheimer's Disease Assessment Scale - cognitive sub-scale

H0b	There is no statistical difference in the score of ADAS-cog before and after HSA $\mu_{ADAS\_differences}=0$ or $\mu_{ADAS\_before}-\mu_{ADAS\_after}=0$
H0b	There is a statistical difference in the score of ADAS-cog before and after HSA $\mu_{ADAS\_differences}\neq0$ or $\mu_{ADAS\_before}-\mu_{ADAS\_after}\neq0$

Estatísticas de amostras emparelhadas

		Média	N	Desvio padrão	Erro padrão da média
Par 1	ADAS_before	30.00	6	11.100	4.531
	ADAS_after	25.33	6	9.136	3.730

Correlações de amostras emparelhadas

		N	Correlação	Sig.
Par 1	ADAS_before & ADAS_after	6	.858	.029

Teste de amostras emparelhadas

		Diferenças emparelhadas					t	df	Sig. (2 extremidade s)
		Média	Desvio padrão	Erro padrão da média	95% Intervalo de confiança da diferença				
					Inferior	Superior			
Par 1	ADAS_before - ADAS_after	4.667	5.715	2.333	-1.331	10.665	2.000	5	.102

Table 17 - ADAS-cog T-test statistics

The correlation obtained from the data is high (0.858), and the significance level is lower than 0.05, leading to the rejection of the null hypothesis - in other words, the correlation between the universe is not zero.
The correlation is significative, and there is a positive linear association between the scores of ADAS-cog obtained on the two measuring moments.

Regarding the T-test analysis, the null hypothesis cannot be rejected. The mean difference is not significative considering a 95% confidence interval (p-value is higher than alpha (0.102>0.05)).

Sample size

Considering 90000 cases os Alzheimer in Portugal, considering a 5% margin of error and a 95% confidence level, we estimate a recommended sample size of 289 cases.

5.4

DISCUSSION

A thorough interpretation of the obtained results leads to several inferences and insights, addressed on the following paragraphs.

5.4.1

Challenges

The following topics epitomize several hindrances that should be taken into account on a following clinical trial:

Recruitment resistance

Insecurity must be pointed out as one possible cause of refusal to participate in the present study.

During the preliminary study and partially due to time restriction issues, the first contact with the participants was established by the main investigator.
Our feeling was that part of the refusals to participate may be due to an absence of previous knowledge of the study from their current physician. Moreover, inviting subjects and explaining the intervention via the phone revealed to be a harsh task. Most of the patients are elderly people, many of them have hearing problems, (a big issue when explaining the experiment via phone) and their are not used to being contacted in order to participate in any studies whatsoever[i].

On a future project, first contact should be addressed by the patient's physician, preferably during a regular appointment on an friendly environment, like the doctor's office.
Personal interview increases the researcher's chances of reducing or even eliminate insecurities, and broadcast a clearer message about the experiment we intend to perform and its vicissitudes.

i As a peculiar note, we mention a specific case, where one of the patients whose wife agreed to incorporate the study, got cold feet hours before the first meeting. She called when we were already arriving at the patient's house, stating that despite having agreed with the study, she was fearful that the investigator might go there, "break into her place and rob her" [sic]... We calmed her down assuring her that it was not the case, and that we didn't intended to frighten her, but if we did and consequently she was insecure, with her permission and since we were already near her house, we would go there and explain the procedure once more and if then she still felt insecure, we would leave.
When we got there, we were being expected by two, very angry, fifty year old men, "defending" this lady.
After one and a half hours of talking, showing permission documents (from the Ethics Committee and the Hospital) and several phone calls later (to the hospital and the patient's neurologist), we were granted authorization to conduct the interview. Even so, we were not able to be with the patient alone, and the tests were conducted in the presence of this (small) crowd.

Setting

At this preliminary study, after the patients recruitment, neurocognitive testing and needle administration took place in each of the patients' house.

The procedures were performed at two separate moments. On the first moment, the subjects executed two neurocognitive tests and needles were applied, and on a second moment, needles were removed and tests were repeated. Each period, since we set foot on the patient's house, through test administration and needle placing or removal, took about 60 to 90 minutes.

If going to the patient's place is certainly more convenient to the subjects, who generally feel more comfortable within this kind of *safe environment*, just among these first batch, patients houses were occasionally 30 or 40km apart of each other, which made appointment scheduling a planning nightmare.

Moreover, some patients gently excused themselves from getting out of bed, and neurocognitive tests had to be performed with patients sometimes lying or seated in bed. If, for most cognitive domains evaluation this poses no problem, when it comes to *Construction Drawing Capacity*, subjects are asked to copy objects they're shown within a piece of paper. Lying in bed against properly seated on a desk or table increases the probability of error within their drawings and therefore the probability of worse test results.

With this in mind, we recommend on further researches, resorting to specialized Alzheimer's Disease[i] nursing homes or Daycare Centers to recruit subjects.
Within these institutions, subjects spend most of the time on daily interchangeable routines, making it easier to administer the tests in a much desired "safe environment", thereby saving precious time.
The fact that we had to travel from one house to another and repeat the procedure again and again between and within subjects, was a very "expensive" time consuming task.

Tests interference

As previously stated, within subjects houses, privacy was in some cases difficult to obtain.

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i Or at least **Neurological Diseases** nursing homes or daycare centers

Performing neurocognitive tests with family and relatives nearby, revealed itself to be a arduous task - some interviews had to be interrupted more than once, in order to advise caregivers that they shouldn't try to help the patient.
This was awkward considering two main reasons: for starters, the patient and caregiver have welcome the investigator within its house, and it is harsh to ask them to stand quiet and not interfere with the answers given by the patient a second time, when they had already been advised previously to the interview of the importance of getting unbiased test results; secondly, we understand that they did try to help the patient, with the best of intentions and it was funny to note that even after advised, some caregivers subtly positioned themselves out of the investigator's eyesight, so that they could better help the patient without being noted.

Neurocognitive tests scoring

The outcome measure of the present study was cognitive function, evaluated by scores obtained from MMSE and ADAS-cog neurocognitive tests.
The reasons behind the choice of these particular tests were already explained on previous chapters, and supported by several authors like Rosen et al. (1984), Peña-Casanova (1997), Harrison et al. (2007), Chaves et al. (2011), among others, from which we emphasize the relatively fast administration time and ease of usage.

Despite the fact that the generality of the tests questions' have an objective scoring outcome, and by so, they remain *easy to score*[i], others, particularly when it comes to ADAS-cog - have not -, demanding a meticulous analysis by experienced reviewers, which had already been noted by Peña-Casanova (1997).

To quote an example, we will consider question *9 - Oral Language*[ii] from ADAS-cog, where the reviewer is asked to valuate the quality of the patient's speech and expression ability during the entire session (see table 18).

i Pass the redundancy

ii The following is translated and adapted from the original - the tests were applied to Portuguese subjects and therefore, the portuguese version was applied

Question 9 - Oral Language	
Valuation (points)	Criteria
0 - No change	*(No change)*
1 - Very Slight change	*One situation where the patient seems to demonstrate difficulty in expressing himself*
2 - Slight Change	*The subject has difficulty between 25 and 50% of total session time*
3 - Moderate Change	*The subject shows difficulty in over 50% of session time*
4 - Moderately Severe Change	*Difficulty shown clearly in over 50% of session time*
5 - Severe Change	*Mutism, the subject produces one or two words but the speech has void content*

Table 18 - Adaptation of question 9 from the Alzheimer's Disease Assessment Scale (GEECD 2007)

At first glance, and on an individual inquiry of *one* particular patient's session, the valuation of question 9 doesn't seem to arouse any subjective doubt, but as one patient is tested after the other, *speech quality differences* interpreted from previous tests, seem to become more or less apparent, meaning that experience with several patients is needed to properly quantify the degrees of speech impairment within AD patients.

In a future trial, it is recommended resorting to experienced psychologists concerning the administration and scoring of neurocognitive tests. In doing so we expected an increase in the precision of the test results.
Also, it is undeniable that the investigator was cheering for better test scores on second interviews. Despite trying to be as objective as possible, we must admit the possibility of some bias having occurred. Therefore, combining experienced reviewers and a double blinded methodology, might result in more precise and unbiased outcome.

Study Compliance

During the three day trial period, patients were advised that needles could eventually fall during that time.
One of the concerns expressed by the subjects and their caregivers regarding the experiment, was related to their personal hygiene - several patients asked if they were allowed to wash their hair, fearing that the needles would fall off, therefore ruining the study.

Retaining the needles was in fact a requirement of the preliminary study, but patients were also told not to alter any of their daily routines, and as such, we didn't intend them to neglect their personal hygiene.

On second interviews, some patients mentioned that needles, or part of them at least, had fallen.
We could clearly understand by the speech of two caregivers (cases 2 and 3) that the actual needles hadn't fallen, but they were removed by the patient in one case or by the caregiver, on the other.

On patient 2, the caregiver stated that all of the needles were removed due to the patient discomfort after day two. Nevertheless, this patient showed a 30% increase on MMSE score and an effective 11% improvement on the score of ADAS-cog.

On patient 3, who had obtained worse results in both tests after day three, a 3% decrease in MMSE, and 3% increase in ADAS-cog[i], the needles were removed right after the first day. We should also note that this patient was deep asleep when we arrived for the second interview, which might have influenced test results.

There was just one case were all the needles were retained until the end of the trial (patient 1). This patient improved in both tests - 27% on MMSE score (8 points) and an effective 20% improvement on cognitive function measured by ADAS-cog (14 points).
We know now, as reported by her daughter, that this lady new she was repeating the tests again in a near future and practiced some questions she still remembered from session 1, like *word recall* and *word finding*.
Also on removal day, before the re-test, the caregiver reported several repetitive questioning from the patient, regarding *which day of the week, month and year* it was - questions that supposedly she also remembered we asked on the first session.

Naturally, at the present time and with retrieved data, there is no support to state whether pre-removal of the needles had or not an effect on test scores obtained

i An increase in ADAS-cog represents an increase in the magnitude of the cognitive impairment

at the end of day three. All patients except one, lost at least one needle during the experiment and even so, only in the case of patient 2 a decrease in cognitive function occurred (supported by both tests scores).

Some questions raised by previous paragraphs include firstly, how important is it to retain the needles, or <all> the needles for a three day period, and secondly, whether those three days represent enough time to avoid bias on neurocognitive test performance due to patient's memory recall of previously performed test.
On future trials, patient recruitment should consider a control group to which sham acupuncture is administered, and a wash out period in case of test repetition to avoid bias.

T-test results analysis

Regarding the applied neurocognitive tests[i], an increase on MMSE points to an improvement on the patient's cognitive function, as does a decrease in ADAS-cog score.

Stein et al. (2012), resorting to Reliable Change Index[ii], found changes of 2 or 3 points on MMSE, of enough magnitude to be considered reliable, indicating an effective cognitive change. On the present study, the computed average change was 3.83 points, indicating a possible positive effect. The same authors also found age and education to be highly influencing factors on MMSE scores. On the present study, only one of the six subjects had higher education, all of the remaining abandoned studies with about the age of nine.

On a future trial, it is recommended to consider these (age and education level) as independent confounding variables, establishing subgroups and thus performing independent analysis.

Comparing these results with those obtained by testing cognitive function efficacy via pharmacological strategy, we observe that Birks (2009), for instance, found a 2 point statistically significant improvement on cognitive function measured on ADAS-cog scale, over the course of 26 weeks treatment with high Rivastigmine dosages on AD patients. Broadening the scope to include other Ach Inhibitors (Donepezil, Galantamine, along with Rivastigmine), the same author

i Mini Mental State Examination & Alzheimer's Disease Assessment Scale

ii A test that determines what is considered a reliable change in test scores - unlikely to have occurred by error or bias

had already previously demonstrated improvements of [negative] 2.7 points on ADAS-cog over the course of 6 month treatments (Birks 2006). And similar results had also already been reported by Kaduszkiewicz et al. (2005). In this case, the investigator identified decreases of 1.5 up to 3.9 points on ADAS-cog with follow ups from 6 weeks up to three years, in AD patients submitted to cholinesterase inhibitors.

Despite some controversy regarding the usage of the MMSE, considered by some an inadequate instrument to detect small changes in cognitive function (Bowie, Branton et al. 1999), this scale is one of the most widely used for that purpose. Bowie et al. computed a true cognitive change in the order of a difference of a minimum of 3 points between observations.
When comparing researches on the efficacy of cognitive changes obtained resorting to Rivastigmine on 6-12mg daily dosages, measured by MMSE, Birks (2009) found improvements of about 0.8 points over the course of 6 months.

FDA[i] and EMEA[ii] consider a change of 4 our more points in ADAS-cog score as representing a significant clinical effect on a clinical trial setting (McGleenon, Dynan et al. 1999). In the scope of this preliminary study, we observed changes of 2 up to -14 points in the 70 point ADAS-cog scale, with average score above that threshold (-4.67). On MMSE differences ranged from -1 up to 9 points.

Chronic effects of HSA were not analyzed over the course of the preliminary study, but considering the obtained results as an acute effect of HSA, MMSE scores increased in average 3.83 points, when comparing values obtained before and after the intervention. That represents an estimated 13% increase on the 30 point test scale. On the other neurocognitive assessment tool, ADAS-cog scores decreased by a mean of 4.67 points, about 7% on the 70 point scale.

Although measured changes of the scores in both tests denote a clear improvement in cognitive function, no statistical evidence was found. Putting aside (for now), methodology issues addressed above, it is our firm believe that one of the main reasons for absence of statistical evidence was the small sample size.

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i Food and Drug Administration

ii Nowadays European Medicines Agency (EMA) formerly know as the European Agency for the Evaluation of Medicinal Products

5.4.2

Proposed Methodology on a future clinical trial

5.4.2.1

Title

Effects of combined therapy (Heidelberg Scalp Acupuncture plus Pharmacological treatment) vs Pharmacological treatment on the cognitive function of Alzheimer's Disease patients

5.4.2.2

Research Team (as in preliminary study)

Main investigator

Carlos Reis, Pharmacist
Degree in Pharmaceutical Sciences
Specialist in Community Pharmacy
Master student in Traditional Chinese Medicine – ICBAS-UP[i].

Co-investigators

Pedro Carneiro, MD
Specialist in Neurology - Hospital Santos Silva, Centro Hospitalar Vila Nova de Gaia/Espinho; Neurology Outpatient Clinic – Hospital da Santa Casa de Misericórdia, Marco de Canaveses.

Nuno Correia, MD
Specialist in Internal Medicine – Emergency Service, Hospital São João, Centro Hospitalar São João, Porto
MSc in Traditional Chinese Medicine

Plus:
Psychologist 1
MSc in Clinic Neuropsychology, Hospital Da Santa Casa da Misericórdia de Marco de Canaveses

i Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto

Psychologist 2

Centro de Dia para Pacientes de Alzheimer São João de Deus - Hospital Conde Ferreira

Research supervision

Main supervisor

Professor Henry Johannes Greten, PhD, MD

Director of the TCM Master Program – ICBAS-UP

Head of the Heidelberg School of Traditional Chinese Medicine;

President of the German Society of Traditional Chinese Medicine (DGTCM[i]), Heidelberg, Germany.

Co-Supervisor 1- Pedro Carneiro (MD).

Co-Supervisor 2 - Nuno Correia (MD).

5.4.2.3

Study Arguments, Objectives and Hypothesis

Arguments

Given the promising results found in the current preliminary study, it is our believe that HSA could have a positive effect on AD patients.

On the previous study, due to several restrictions, we worked with a small sample of patients and we were given the chance to identify several methodological glitches.

In this proposed clinical trial, we take advantage of our current experience to improve methodology and carry on our previous research.

Objectives

To evaluate the efficacy of Heidelberg Scalp Acupuncture (HSA) on the cognitive function of Mild to Moderate Alzheimer's Disease patients. This will be achieved by comparing the changes measured in ADAS-cog and MMSE, obtained from patients submitted to combination therapy (HSA plus regular pharmacological

i on the original - *Deutsche Gesellschaft für TCM*

therapy) versus patients performing regular pharmacological therapy.

Expected Results

As before, we expect that HSA positively contributes to improve cognitive function in patients with Alzheimer's Disease. From previous research, it is also expected that these effects will be more pronounced among patients diagnosed with Mild to Moderate stages of the disease.

Research question

Are there any significative differences in cognitive function of Mild to Moderate AD diagnosed patients, when they are subjected to HSA in addition to their pharmacological therapy?

Study hypothesis

Experimental Group: subjected to HSA + Pharmacological therapy
Control Group: Pharmacological therapy

H0: There is no statistical difference in cognitive function between experimental and control groups
H1: There is a significative difference between cognitive function of experimental and control group

5.4.2.4

Setting

Pre Experimental Procedure - Recruitment and Design

Sample and Recruitment

This study will be focused on Portuguese individuals, with ages between 40 and 90, diagnosed with Mild or Moderate stages of Alzheimer's Disease.

Patients recruitment relay on an independent co-investigator approval, based on the patients clinical chart and eligibility criteria (table 8).

Regarding patient recruiting, we will resort to Nursing Homes and Specialized Alzheimer's Daycare Centers.

At the present moment, after granted Ethical Committee approval, the project will be proposed to both Nursing Home da Santa Casa da Misericórdia de Marco de Canaveses and to the Centro de Dia para Pacientes de Alzheimer e outras Demências São João de Deus, belonging to Hospital Conde Ferreira. In the meanwhile, other institutions will be contacted in order to assess their availability.

AD diagnose is performed by Dr. Pedro Carneiro, Neurologist, and the neuropsychological tests administered with the cooperation of experienced psychologists.

Inclusion criteria	**Exclusion criteria**
1-Male or female patients, 40 to 90 y.o., with confirmed diagnosis of Alzheimer's Disease, Possible or Probable according to the diagnostic criteria of the DSM-V and NINCDS-ADRA (American Psychiatric Association - DSM-5 Task Force 2013) (McKhann, Drachman et al. 1984) *2-Neurocognitive MMSE test score between 10 and 24 (moderate AD: 10-18; mild AD: 19-24)* *3-Patients under stable pharmacological conventional treatment (> 3 weeks)* *4-Informed consent signed by patient or legal substitute.*	*1-Diagnosis of mixed Dementia and Alzheimer's Disease, or other Dementia type besides Alzheimer* *2-Previous brain lesions that may influence cognitive function.* *3-Epilepsy or other neurological chronic disease.* *4-Any acute disease* *5-Unstable at-risk patient* *6-Hematological disease*

Table 8 - Eligibility criteria

After the initial screening, potential participants are contacted, or when necessary, their families or caregivers to schedule an appointment in the presence of both the main investigator and the co-investigator.

Within this initial interview, the general goals of the study are explained to the patient and family/caregiver, the procedures are scrutinized and any doubt is thoroughly clarified. Only then, the invitation for the patients to participate in the study is proposed, and on positive feedback, informed consents are presented.

Sample size

Sample size was calculated based on previous preliminary study, resulting in a total of 289 subjects needed.

Sample randomization

After recruitment, a serial number based on the study's entry date is attributed to each participant, and the sample is randomly divided into two groups using Excel™ random numbers function.

Outcome assessment

The primary outcome of the present study is Cognitive Function, measured by neurocognitive assessment tools[i]. Reasons to support the choice of MMSE and ADAS-cog are, first of all, its validity and sensitivity to measure cognitive change, the existence of scientific literature to support its usage, their relative ease of usage (whether in terms of test administration and also completion time) and experience of the co-investigators in its application and scoring.
Administration and scoring of the neurocognitive tests will be performed by experienced psychologists.

Study design

The study design is a randomized, multi-centric, controlled, cross-over design (Figure 4).

The crossover design was chosen in order to reduce inter-individual variability when comparing control versus the experimental group, as well as to increase the number of cases.

A three week wash-out period will be established to avoid carry over effects of HSA on the evaluation of the patients between intervention phases.

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i Referring to the US Food and Drug Administration, requirements needed for AD clinical drug trials efficacy assessment, are, first of all - improvement on a performance based cognitive instrument and second - proof that the improvement is clinically meaningful

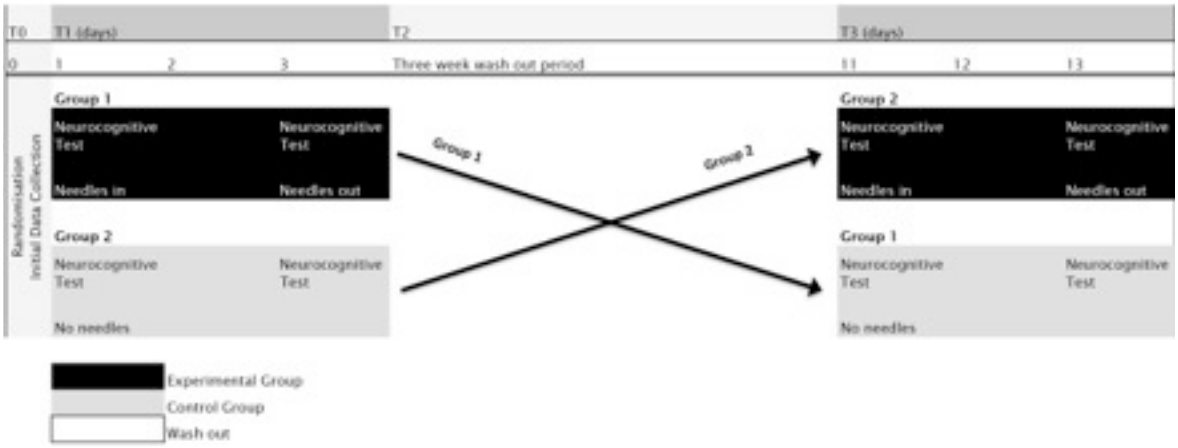

Figure 4 – Experiment Design plan

Collected patients data

At Baseline (T0)

Name, Age, Gender, Educational Background, Time of Onset of the disease and Current Medication.

At test period (T1 & T3)

Previously and after the three day intervention periods, neurocognitive tests were performed for each subject, and their outcome recorded.

During the experiment

At any given time during the experiment, drop off reasons, adverse effects as well as general feelings towards the procedure were collected.

Experimental procedure - Intervention

The experimental protocol is based on the clinical experience from the Heidelberg Clinic of Chinese Medicine workgroup, and on results from our preliminary study, concerning the treatment of AD patients with HSA.

As on the preliminary study, we again propose the placement of 7 semi-permanent scalp acupuncture golden needles in the skull, within the area of the so called *seven chakras* and retaining them for a three day period.
Concerning the exact position of the needles, the reference point is located in the apex of the head, on the point described in literature as GV20, obtained from the intersection of two imaginary lines going from: the first - the tip of the ear lobe and the vertex, through the top of the skull, back to the other ear vertex and

lobe; and the second - from the tip of the nose to the tip of the occiput. Each of the six remaining needles were placed respectively one Scalp Acupuncture *cun* distant from the previous, in the direction of the forehead.

The actual needling will be performed by the main investigator under medical supervision, and no twisting, twirling, pulling or any other technique was applied to the needle until their removal in day 3, after which neurocognitive tests were repeated.

While placing and removing the needles, patients should be comfortably seated in a resting chair, within an office gently provided by the respective hospital.

In the cases where the needles fall during the test period, they were to be replaced as soon as noted.
No other recommendation is made to the clinical staff regarding the patients daily routines, besides the fact to avoid any changes in their usual medication during the trial duration, if possible.

The experimental procedure is performed for the Experimental Group at T1, while at the same time, the remaining patients act as Control Group, and vice versa at T3.
A three week wash out period, (T2), was imposed between T1 and T3, with the objective to reduce any probability of occurrence of cognitive effects from previously administered procedures (figure 4).
Neurocognitive tests will be administered to every subject before and after intervention periods.

6

CONCLUSION

"it depends, we have good days and some bad days, when he/she wakes up we'll see"

Maybe eight out of ten times, this is the answer we get when you ask any caregiver or family member of an Alzheimer's Disease patient [as we did] - *How do you think he/she is progressing?*

One of the key aspects of Alzheimer's Disease is the progressive deterioration of both cognitive and non-cognitive functions. Brain activity and memory become more and more impaired as the disease progresses, corroborating the patient's either suspicious or oblivious attitude towards life, categorically perceivable in later stages of the disease.

Diagnose is complex and definite verdict is only confirmed as a result of post-mortem biopsy of brain tissue. Despite all the majestic scientific advances since its discovery in the turn of the 19th century, by the german psychiatrist *Aloysius Alzheimer*, there is actually no cure for AD.
Therapeutic measures include any reasonable technique that might be used to improve the patient's quality of life, granting any bit of the stollen autonomy the patient once had, usually encompassing neurocognitive stimulation and of course, the use of pharmacological agents.
But within this intricate symptomatological picture, demential diseases are unforgiving pathologies, that even when resorting to any therapeutical weapon available, uncover real human life misery - if treating the cognitive deficit points to a well defined pharmacological class of drugs like acetylcholinesterase inhibitors, cerebral vascular dilating agents, or plain nootropics, the array of diverse symptoms that arouse with the disease, make these patients strong candidates for a *"who takes more pills a day"* contest. Hallucinations, agitation anxiety and emotional disturbances affect a huge percentage of AD patients, meaning that antipsychotics, anticonvulsants, antidepressants and anxiolytics are usual within these patients daily pharmacological schemes (Sink, Holden et al. 2005), not to speak of medicines used to overcome common chronic elderly diseases like high blood pressure, diabetes, pulmonary obstructive diseases, among others.
Given this circumstances, comprising polimedicated elderly individuals with a somewhat feeble condition, neurocognitive testing demands rigorous scientific

design.
In this sense, methodological glitches of this preliminary study, were pointed out in the previous chapters to the best of our observation. Larger, segmented samples are needed, preferably in a controlled testing setting.

Whether HSA acts by limiting the breakdown of acetylcholine, or by any other auxiliary mechanism such as the activation of functional brain connectivity areas, (as other investigators have demonstrated regarding acupuncture), or even increasing cerebral vascular perfusion, will remain an unsolved mystery after the present study and a challenge for future researching teams. However, in our moderate opinion, the increases measured in this preliminary study, are not to be neglected.
Despite our failure to achieve proven scientific evidence, Heidelberg Scalp Acupuncture showed promising results on the reversion of the cognitive deficit felt by AD patients, demanding a new paradigm approach.

After these results, we expect to have raised in the scientific community, a little curiosity sparkle that leads to future and better designed clinical trials.

If we can prove that Heidelberg Scalp Acupuncture has a significative effect on reverting the course of the disease, we would be positively contributing to a better life of those who suffer from a disease which has been growing exponentially over the last decades.

-Is there any greater challenge?

7

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8

ANNEXES

Annex 1 - ICBAS-UP Ethical Committee approval form

Comissão de Ética

U.PORTO

INSTITUTO DE CIÊNCIAS BIOMEDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Parecer da Comissão de Ética do ICBAS-UP

PROJETO Nº 72/2014

Título: *Estudo da eficácia da Terapia Combinada (Terapia Convencional Farmacológica + Craniopunctura) no tratamento da doença de Alzheimer*
Investigadora Responsável: Carlos Miguel Soares dos Reis
Orientador: Professor Doutor Henry Greten
Duração do Projeto: até março de 2015

A Comissão de Ética do ICBAS-UP reuniu dia 03 de julho de 2014 no edifício do ICBAS - Sala de reuniões do Departamento de Ciências do Comportamento, na presença de Liliana de Sousa, Manuel Vilanova, Margarida Araújo, Maria Antónia Gonçalves e Paulo Maia. Decidiu emitir parecer favorável à realização do projeto supracitado, por unanimidade.

Solicitamos que envie anualmente a esta Comissão um resumo dos resultados obtidos na sequência deste projeto.

Com os melhores cumprimentos,

Pela Comissão de Ética do ICBAS-UP,

Prof. Doutora Liliana de Sousa (presidente)

To whom it may concern,

The above project is in accordance with the Portuguese law and the ICBAS-UP Ethics Committee criteria.

SANTA CASA Misericórdia de Marco de Canaveses
FUNDADA EM 1934, POR VALORES

Declaração

Maria Amélia Duarte Ferreira, Provedora da Santa Casa da Misericórdia do Marco de Canaveses, declara para os devidos efeitos que o " Estudo da Eficácia da Terapia Combinada (Terapia Convencional Farmacológica + Acupunctura /Craneopunctura) no Tratamento da Doença de Alzheimer", integrado no Mestrado em Medicina Tradicional Chinesa do Instituto de Ciências Biomédicas de Abel Salazar da Universidade do Porto, seja realizado pelo estudante de mestrado Carlos Miguel Soares dos Reis, na Santa Casa da Misericórdia do Marco de Canaveses., sob a orientação do Dr. Pedro Carneiro, neurologista da SCMMC.

Marco de Canaveses 23 de Julho de 2014

Provedora

Professora Doutora Maria Amélia Ferreira

Alameda Dr. Miranda da Rocha, 90 - 4630-200 Marco de Canaveses • Tel. 255 538 300 - Fax 255 534 541 • Pessoa Colectiva **500 746 761**

Participação em Projecto de Investigação

Consentimento Informado, Livre e Esclarecido

Este modelo respeita a Declaração de Helsínquia[1] e a Convenção de Oviedo[2]

Por favor, leia atentamente a seguinte informação.

Se achar que algo está incorreto ou que não está claro, não hesite em solicitar mais informações.

Se concorda com a proposta que lhe foi feita, queira por favor assinar este documento.

Título do estudo

Estudo da eficácia da Terapia Combinada (Terapia Convencional Farmacológica + Craniopunctura) no tratamento da doença de Alzheimer

Enquadramento

O presente estudo é realizado como parte integrante da tese de Mestrado em Medicina Tradicional Chinesa de **Carlos Miguel Soares dos Reis**, ministrado pelo Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto.
A orientação do projecto cabe ao Exmo. **Prof. Doutor Henry J. Greten** – Professor do Mestrado de Medicina Tradicional Chinesa no Instituto de Ciências Biomédicas Abel Salazar - UP; Director Clínico do "Institute for Chinese Medicine", Heidelberg, Alemanha, Especialista em Medicina Familiar, Naturopatia, Homeopatia e Acupunctura, pela Ordem dos Médicos, Alemanha, na qualidade de **Orientador** e ao Exmo. Sr. **Dr. Pedro Carneiro**, Médico especialista em Neurologia, na qualidade de **Responsável Clínico**.

Proposta

O projecto apresentado resulta de um trabalho de pesquisa e recolha de informação de investigações anteriores e o procedimento proposto foi pensado e simplificado por forma a causar o menor distúrbio possível nas rotinas diárias dos participantes.

Em estrita coordenação com o **Dr. Pedro Carneiro**, propõe-se a pacientes diagnosticados com doença de Alzheimer, a adição de um protocolo de craniopunctura ao seu regime terapêutico habitual.

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[1] http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

[2] http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

Explicação do estudo

O que é a acupunctura/craniopunctura?
A acupunctura é um ramo da Medicina Tradicional Chinesa e uma técnica terapêutica reconhecida pela Organização Mundial de Saúde (OMS) como Método de Tratamento Complementar, recomendada por esta Instituição para o tratamento de uma variedade de patologias entre as quais as Demências, da qual faz parte a Doença de Alzheimer.

Esta técnica, desenvolvida há mais de 3000 anos, consiste na aplicação de agulhas estéreis em determinados pontos localizados na superfície corporal, chamados de pontos de acupunctura ou acupontos. Quando esses pontos se localizam especificamente na zona da cabeça, toma o nome de craniopunctura.

[A acupunctura corresponde a uma técnica terapêutica amplamente utilizada no âmbito da Medicina Tradicional Chinesa, que consiste na aplicação de agulhas estéreis em determinados pontos localizados na superfície corporal.
A Craniopunctura é uma técnica de somatotopia, baseada num sistema de acupontos que estão funcionalmente correlacionados com regiões cerebrais. As agulhas utilizadas neste caso são semi permanentes, de 0,16mm de diâmetro por 3,4,5 ou 7mm de comprimento.
O procedimento é razoavelmente simples e a maioria dos pacientes não sentem desconforto salvo uma leve sensação de picada, que geralmente desaparece ao fim de alguns segundos.]

Qual o procedimento metodológico?
Caso autorize a participação neste projecto, o paciente será aleatoriamente englobado num de dois grupos experimentais, aos quais serão administrados protocolos de craniopunctura.
O protocolo consiste na inserção de agulhas de craniopunctura em zonas específicas do corpo.

Descrição cronológica do estudo

Antes de iniciar o protocolo experimental, irá proceder-se à recolha de dados referentes aos pacientes que acedam participar do estudo.

Posteriormente os pacientes serão aleatoriamente divididos em dois grupos.

A cada um desses grupos, irá administrar-se em período distinto, o respectivo protocolo experimental.

O protocolo consiste na aplicação de agulhas semi-permanentes de craniopunctura descritas acima, que deverão permanecer aplicadas durante um período de três dias. Antes e depois desta administração serão realizados os testes de avaliação neurocognitiva não invasivos.

Nenhuma outra alteração será efectuada na vida activa do paciente no âmbito do presente estudo, salvo as claramente explicitadas. Este continuará a ser acompanhado pelo seu médico responsável e a seguir as suas indicações terapêuticas.

Qual o local onde serão realizados os tratamentos?
O local onde se procederá à aplicação do protocolo, será aquele que mais convier às necessidades do paciente, responsabilizando-se o investigador por todas as deslocações que venham a ter lugar no âmbito do presente estudo.

Quais são os riscos que posso esperar?
Quaisquer dos procedimentos descritos anteriormente, (acupunctura/craniopunctura), são razoavelmente simples e a maioria dos pacientes não sentem desconforto. Exceptua-se a inevitável a sensação de picada que advém da inserção da agulha, que geralmente desaparece ao fim de alguns segundos. Pode ocorrer um ligeiro sangramento na remoção das agulhas, considerado também normal.

Quanto tempo dura o estudo?
Está previsto uma duração aproximada de duas a três semanas para a realização do estudo.
Um primeiro bloco decorrerá no espaço de três dias após a entrada dos pacientes para o estudo, após o qual se seguirá um período de wash out de uma semana, seguida de novo período de três dias para inverter os testes de sujeitos.

Há garantias quanto ao resultado esperado?
O presente estudo está devidamente fundamentado noutras investigações científicas anteriores e propõe testar uma nova abordagem para o tratamento da condição patológica do paciente, mas como em qualquer estudo experimental, nenhuma garantia poderá ser dada ao paciente ou à sua família, quanto à resolução efectiva do problema de saúde.

Posso abandonar o estudo a qualquer momento?
Sim.
Embora a sua participação seja fundamental para a nossa investigação, não há nenhum "vínculo" objectivo que obrigue o paciente a permanecer no estudo durante o seu período de realização.

Qual a importância da sua participação?
Ao participar neste estudo, estará a contribuir para o desenvolvimento da ciência nesta área do conhecimento.

Condições e financiamento
Este estudo não é financiado por qualquer instituição ou empresa, sendo os custos resultantes da sua produção, totalmente suportados pelo próprio investigador.
A participação é de carácter voluntária e o estudo mereceu o parecer favorável da comissão de ética do ICBAS - UP e do seu orientador.
Qualquer ocorrência não prevista é, antes de mais, responsabilidade do investigador, e depois, da Escola de Medicina Chinesa de Heidelberg - Heidelberg School of Chinese Medicine -, sita em Karlsruher Straße 12, 69126 Heidelberg-Rohrbach, Alemanha, com os contactos telefónicos e electronico, respectivamente 06221-374546, heidelbergschool@aol.com.

Confidencialidade e anonimato
Os dados recolhidos no âmbito desta investigação são confidenciais, sendo em toda a altura preservado o anonimato dos seus participantes. Os dados serão mantidos unicamente durante o período necessário à realização da experiência e produção do documento de investigação.

Em meu nome, Carlos Miguel Soares dos Reis, agradeço de forma sincera a sua participação

Assinatura:

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela/s pessoas/s que acima assinam e que considero suficientes.

Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências.

Desta forma, aceito participar neste estudo e permito a utilização dos dados que de forma voluntária forneço, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelo investigador.

Utente: _____

Consentidor: _____
(Deverá anexar documento a atestar a representação legal do utente)

Data: __ /__ /_____

Assinatura:

Este documento, composto de 5 página/s, é feito em duplicado - uma via para o/a investigador/a, outra para a pessoa que consente

DECLARO, PARA OS DEVIDOS EFEITOS, QUE O PACIENTE REFERENCIADO NA PÁGINA ANTERIOR, ESTÁ LEGALMENTE A MEU CARGO.

Nome em caligrafia legível

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Assinatura

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Orientação do Projeto de Investigação:

Prof. Doutor Henry J. Greten – Director do Mestrado em Medicina Tradicional Chinesa no Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto; Director Clínico do "Institute for Chinese Medicine", Heidelberg, Alemanha, Especialista em Medicina Familiar, Naturopatia, Homeopatia e Acupunctura, pela Ordem dos Médicos, Alemanha, na qualidade de orientador de Carlos Miguel Soares dos Reis, declaro que concordo com os objetivos e metodologias propostas no âmbito do projeto "**Estudo da eficácia da Terapia Combinada (Terapia Convencional Farmacológica + Acupunctura) no tratamento da doença de Alzheimer".**

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Porto, 4 de Abril 2014

Orientador

Prof. Henry J Greten

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ICBAS - UP